The role of long noncoding RNA H19 in gynecological pathologies: Insights into gene regulation and immune modulation (Review)

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Abstract. Long non-coding RNAs (lncRNAs) represent a class of versatile molecules that exhibit the potential to regulate gene expression at various levels, namely transcriptional, post-transcriptional and epigenetic, thereby influencing critical cellular processes such as proliferation, apoptosis, invasion and drug resistance. The lncRNA H19, among the earliest identified within this category, has emerged as a significant participant in the pathogenesis of a multitude of both malignant and benign gynecological diseases. An escalating body of evidence indicates a functionally pertinent network of lncRNA H19 coexpression linked with the extracellular matrix architecture and immune microenvironment during cancer progression. This association may provide insightful leads for the selection of innovative diagnostic biomarkers and assist in the delineation of potent pharmaceutical targets for gynecological oncology. The present comprehensive review presented a synthesis of the expression profiles and multifaceted implications of lncRNA H19 across a spectrum of gynecological pathologies.

Contents

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1. Introduction

Long non-coding RNAs (lncRNAs) represent a distinct class of noncoding RNAs (ncRNAs) that exceed 200 nucleotides in length and have been found to modulate cell proliferation, apoptosis, invasiveness, drug resistance, and other pivotal biological functions. These functions can be influenced at the transcriptional, posttranscriptional, and epigenetic levels (1,2). Numerous investigations in recent years have underscored the critical role lncRNAs play in multiple stages of disease pathogenesis (3). Among the early identified lncRNAs, lncRNA H19 has been garnering significant interest across a variety of disciplines. This review provides a comprehensive overview of the characteristics and recent advancements in research pertaining to lncRNA H19 in the field of gynecology.

2. Overview of lncRNA

Definition and function of lncRNA. The most recent update from the human GENCODE project (accessible online: https://www.gencodegenes.org/) reveals that a mere 34.09% of the total human genes, numbering 19,901, encode proteins (4). The broad category of RNA is bifurcated into messenger RNA (mRNA), capable of protein encoding and ncRNA, which lacks this capability. lncRNA, defined by a length exceeding 200 nucleotides and absence of an open reading frame for protein translation, forms the majority within the ncRNA category (5). lncRNAs share several defining characteristics (6): i) The chromatin states of their coding genes, particularly in relation to promoter H3K4me3 and transcription region H3K36me3, mirror those of protein-encoding genes; ii) Their expression is governed by a diverse array of shared transcription factors; iii) As with protein-encoding genes, lncRNAs are transcribed by RNA polymerase II, typically undergo spliceosomal splicing and possess polyadenylated tails.

Historically, lncRNAs were considered functionally irrelevant, mere 'noise' in the process of gene transcription. However, advances in genome splicing array analysis and high-throughput transcriptomic sequencing have revealed that lncRNAs are not genomic byproducts, but are involved in numerous physiological processes, affecting vital biological functions such as cell proliferation, differentiation, chromosomal remodeling, epigenetic regulation, transcription and

posttranscriptional modification (7-11). Hence, the potential involvement of lncRNAs in human diseases has attracted considerable research interest. Despite the identification of over 8,000 different types of lncRNAs through the human genomic project, only a limited subset of ~200 lncRNAs has been extensively studied (12). The majority of lncRNAs have been found to reside in the nucleus, cytoplasm and organelles (primarily the nucleus) and their expression displays marked tissue- and time-specificity, along with significant variability across different tissues, within different regions of the same organ and across different disease stages (13-15).

Classification and biological mechanisms of lncRNAs. lncRNAs can be categorized based on several criteria. Functionally, they are segregated into cis-lncRNAs and trans-lncRNAs (16). Genomically, lncRNAs can be classified according to the location of the encoding DNA fragment as intragenic lncRNAs, intergenic lncRNAs, divergent lncRNAs, antisense lncRNAs, or enhancer lncRNAs (17). In terms of temporal and functional characteristics, lncRNAs can be divided into transcription-regulating lncRNAs and posttranscription-regulating lncRNAs (18).

Presently, lncRNA studies predominantly focus on data mining and functional verification. Data mining studies employ methods such as lncRNA microarray detection, library construction based on ribosomal RNA (rRNA) removal, lncRNA-seq and high-throughput sequencing. Functional verification studies, on the other hand, involve *in vitro* cell-based assays and *in vivo* animal model experiments (19). lncRNAs exert their biological effects via several mechanisms, which include: i) Gene transcription regulation: lncRNAs can repress gene transcription by forming complementary sequences with gene promoters, or they can stimulate gene transcription by binding to the enhancers of proximal protein-coding genes; ii) Posttranscriptional processing: lncRNAs can influence mRNA splicing patterns by forming double-stranded RNA through pairing with pre-mRNA. Additionally, lncRNAs can modulate mRNA splicing by regulating the activity of splicing factors (20); iii) Translation regulation: lncRNA can function as a competitive endogenous RNA (ceRNA) of microRNA (miRNA/miR) to modulate mRNA expression levels, thereby effecting the translation of downstream proteins (21,22); and iv) Epigenetic modification regulation: lncRNAs can recruit chromatin modification complexes to facilitate epigenetic modifications, leading to altered target gene expression (23-25).

3. Multifaceted role of lncRNA H19

Structure and biological function of lncRNA H19. The lncRNA H19 gene, found at the locus 11p15.5 on human chromosome and at the terminus of chromosome 7 in mice, lies ~90 kilobases (kb) distant from the insulin-like growth factor 2 (IGF-2) gene. This gene extends over 2.5 kb, encompassing 5 exons and 4 introns and forms a secondary structure of 16 helices and several hairpin configurations (26). The lncRNA H19 gene transcribes an RNA molecule of 2.3 kb length with 35 open reading frames. Notably, this RNA molecule does not engage in RNA transcription and translation processes, thus being incapable of protein encoding. Therefore, this molecule is classified as a lncRNA and referred to as lncRNA H19 (25,26).

lncRNA H19, one of the earliest discovered and most extensively studied lncRNAs, exhibits significant conservation across evolutionary species. It expresses maternal allelic dominance and paternal imprinting, with the imprinting regulatory region or differentially methylated region located 4 kb upstream, modulating its expression and biological processes (26).

Predominantly, lncRNA H19 expression is pronounced in embryonic and placental tissues, particularly in endodermal and mesodermal derivatives during embryonic development. This pattern implies the pivotal role of lncRNA H19 in embryogenesis and fetal growth (27,28). Postnatal expression of lncRNA H19 diminishes significantly but maintains a residual level in select tissues, including breast, uterus, myocardium, skeletal muscle and the adrenal gland (29-34). During tissue regeneration or tumorigenesis, lncRNA H19 function reactivates, participating in damage regulation and repair, or acting as either a tumor suppressor gene or an oncogene (35,36). Furthermore, the expression of lncRNA H19 positively correlates with the infiltration of various immune cells such as CD4+ T cells, CD8+ T cells, B cells, dendritic cells, neutrophils and macrophages, as well as with diverse immune markers in malignant tumors (37). Thus, lncRNA H19 probably serves a critical role in malignant tumor genesis and progression, offering insights for the identification of novel diagnostic biomarkers and the development of targeted therapeutics (Fig. 1).

Research progress of lncRNA H19. In recent years, investigations into lncRNA H19 have witnessed significant advancements across various diseases. The majority of these studies concentrated on the mechanistic role of lncRNA H19 in tumorigenesis, metastasis and drug resistance, particularly focusing on the lncRNA H19-miRNA regulatory network (Table I).

One notable study reported elevated lncRNA H19 and decreased miR-326 expression in a liver cancer cell line. Bioinformatics analysis revealed that lncRNA H19 regulates cell growth, migration and invasion by targeting Twist-related protein 1 (TWIST1), a downstream target of miR-326, acting as a ceRNA for miR-326. Consequently, the lncRNA H19/miR-326/Twist1 axis was confirmed as instrumental in the pathogenesis of liver cancer (38). A separate study by Ye *et al* (39) proposed that lncRNA H19 fosters hepatocellular carcinoma (HCC) invasiveness by triggering and activating the miR-193b/MAPK1 axis, thereby mediating interplay between HCC and its immune microenvironment.

Epithelial-mesenchymal transition (EMT) serves an indispensable role in malignant tumor pathogenesis, mainly disrupting cell adhesion and facilitating tumor metastasis. Li *et al* (40) demonstrated that the lncRNA H19/miR-194-5p/Forkhead box protein M1 axis influences EMT, contributing to colorectal cancer progression via a series of gene knockdown and overexpression experiments. Furthermore, Ding *et al* (41) discovered that the lncRNA H19/miR-29b-3p/progranulin axis encourages EMT in colorectal cancer cell lines by modulating the Wnt signaling pathway. However, the potential interaction between these two pathways remains uncertain, necessitating further research.

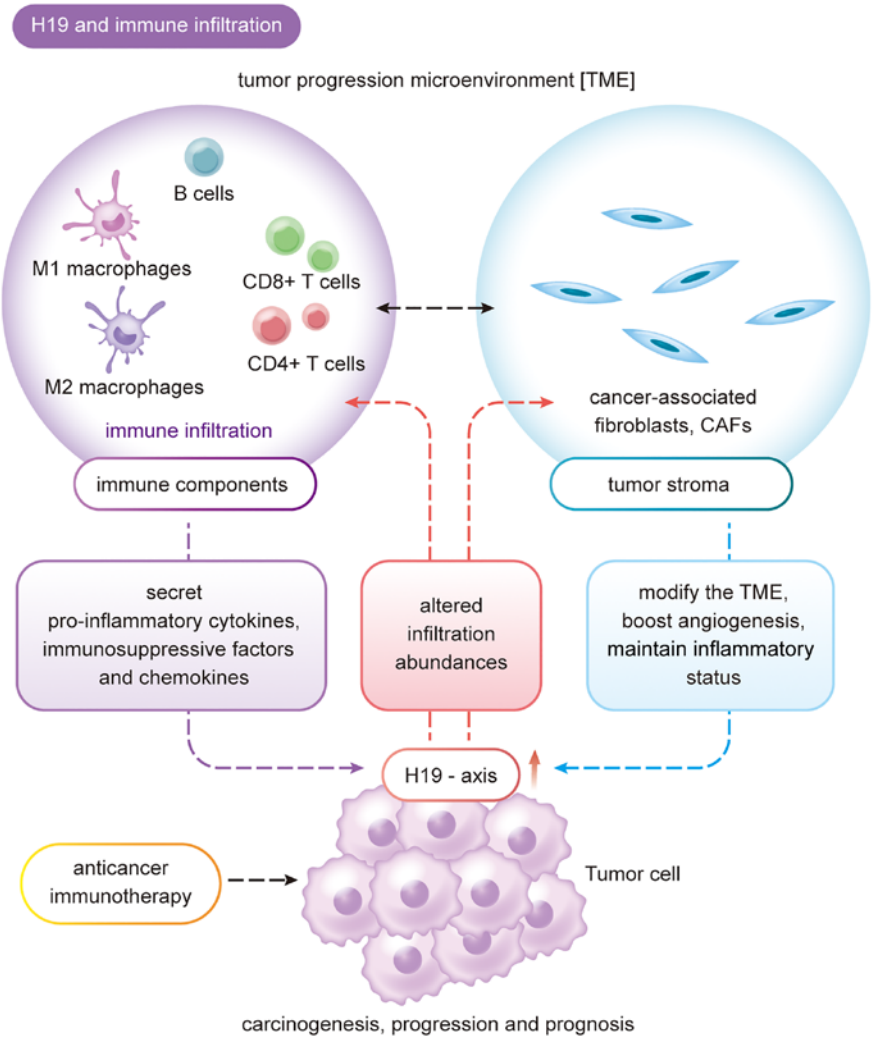

Figure 1. Involvement of lncRNA H19 in the pathogenesis and progression of malignant neoplasms via immune cell infiltration mechanisms. lncRNA, long noncoding RNA; CAFs, cancer-associated fibroblasts; TME, tumor microenvironment.

In a groundbreaking study, Chen *et al* (42) elucidated that lncRNA H19 inhibits vitamin D receptor expression by modulating miR-675-5p, potentially explaining resistance to 1, 25 (OH) 2D3 in advanced colon cancer. Concurrently, numerous studies on other malignancies, including bladder, breast, glioma, melanoma, lung, gastric, renal cancers and leukemia, demonstrated that lncRNA H19 regulates the biological functions of downstream target genes by competitively binding with miRNA, thereby affecting the immune infiltration level and contributing to the poor prognosis of malignant tumor patients. Thus, lncRNA H19 has been identified as a promising new target for immunotherapy (43-51).

By contrast, lncRNA H19 can also serve as a tumor suppressor, impeding metastasis in certain malignancies. One seminal study showed reduced expression of lncRNA H19 and miR-675 in prostate cancer, particularly in M12 cell lines with high tumorigenicity and metastatic potential. lncRNA H19 was found to affect cell migration by modulating miR-675, significantly inhibiting cell metastatic ability following lncRNA H19 overexpression. Subsequent double luciferase analysis demonstrated that miR-675 could bind with the 3' end of transforming growth factor β inducing protein (TGFβI) mRNA, inhibiting its translation. Hence, lncRNA H19 regulates the translation process of TGFBI by modulating miR-675, thereby suppressing the metastasis of prostate cancer (52). Another study revealed a higher lncRNA H19 level in liver cancer tissues compared with adjacent normal tissues. In this context, lncRNA H19 was shown to bind to the hnRNPU/PCAF/RNAPol II protein complex, thereby activating the miRNA-200 family, affecting EMT and consequently, inhibiting metastasis (53).

Research pertaining to lncRNA H19's role in benign diseases remains limited. In patients with sepsis, serum levels of lncRNA H19 and aquaporin 1 (AQP1) were significantly diminished, concomitant with increased miR-874 levels (54). The expression of lncRNA H19 was negatively correlated with miR-874 and positively correlated with AQP1. Moreover, the upregulation of lncRNA H19 significantly reversed the abnormal expression of miR-874 and AQP1, as well as lipopolysaccharide-induced anti-inflammatory cytokine secretion and myocardial dysfunction in cardiomyocytes. Idiopathic pulmonary fibrosis, characterized by pulmonary fibroblast aggregation and extracellular matrix deposition, was associated with increased lncRNA H19 expression in fibroblast proliferation induced by transforming growth factor-1 (TGF-1) and bleomycin-induced pulmonary fibrosis (55). lncRNA H19 was found to target collagen, type I, α 1 by acting as a

Table I. Long non-coding RNA H19 and its targeted microRNAs acting as competitive endogenous RNAs.

First author, year	Disease	MicroRNA	Target gene	Regulation (microRNA/ target gene)	(Refs.)
Wei, 2019	Hepatocellular carcinoma	miR-326	Twist1	Down/Up	(38)
Li, 2018	Colorectal adenocarcinoma	miR-194-5p	FoxM1	Down/Up	(40)
Ding, 2018	Colorectal cancer	miR-29b-3p	PGRN	Down/Up	(41)
Lv, 2017	Bladder cancer	miR-29b-3p	DNMT3B	Down/Up	(43)
Xiong, 2020	Breast cancer	let-7	LIN28	Down/Up	(44)
Luan, 2018	Malignant melanoma	miR-106a-5p	E2F3	Down/Up	(46)
Zheng, 2019	Lung cancer	miR-675-5p	p53	Down/Up	(47)
Sun, 2021	Gastric cancer	let-7	LDHA	Down/Up	(48)
He, 2017	Renal carcinoma	miR-29a-3p	E2F1	Down/Up	(49)
Zhao, 2017	Acute myelocytic leukemia	miR-19a,b	ID2	Down/Up	(50)
Sun, 2019	Pancreatic cancer	miR-194	PFTK1	Down/Up	(51)
Zhu, 2014	Prostate cancer	miR-675	TGFBI	Up/Down	(52)
Fang, 2018	Sepsis	miR-874	AQP1	Up/Down	(54)
Lu, 2018	Pulmonary fibrosis	miR-196a	COL1A1	Down/Up	(55)

miR, microRNA; Twist1, twist-related protein 1; FoxM1, forkhead box protein M1; PGRN, progranulin; DNMT3B, DNA methyltransferase 3 β; LIN28, lin-28 homolog A; E2F3, transcription factor E2F3; LDHA, lactate dehydrogenase A; E2F1, transcription factor E2F1; ID2, DNA-binding protein inhibitor ID-2; PFTK1, serine/threonine-protein kinase PFTAIRE-1; TGFBI, transforming growth factor β induced protein; AQP1, aquaporin 1; COL1A1, collagen, type I, α 1.

ceRNA for miR-196a. The downregulation of lncRNA H19 was found to ameliorate fibroblast activation and pulmonary fibrosis, affirming the critical regulatory role of lncRNA H19 and its potential as a prognostic indicator in idiopathic pulmonary fibrosis (55). Similarly, liver-specific lncRNA H19 was discovered to enhance the enrichment of CD3+γδ+, interleukin-4 and interleukin-17 producing CD4+ and CD8+ immune cell populations in the livers and spleens of lncRNA H19-BDL mice. This mechanism is facilitated through the zinc finger E-box-binding homeobox 1 (ZEB1)/epithelial cell adhesion molecule signaling pathway, leading to cholestatic liver fibrosis (56).

In conclusion, the biological significance of lncRNA H19 extends across a multitude of physiological and pathological processes. It is involved in embryonic development, tissue regeneration, tumorigenesis, immune cell infiltration and serves a role in both malignant and benign diseases. Furthermore, lncRNA H19 demonstrates both oncogenic and tumor-suppressive properties, depending on the specific cellular context. It is clear that a more profound understanding of the regulatory networks involving lncRNA H19 could potentially unlock novel therapeutic strategies for a wide array of diseases, ranging from benign conditions to malignant tumors. However, given the current state of research, further studies are necessary to conclusively elucidate the versatile and context-dependent roles of lncRNA H19 in gynecological pathologies.

4. lncRNA H19 and gynecologic malignancies

lncRNA H19 and cervical cancer. Cervical cancer, a common gynecological malignancy, exhibits the highest incidence in China, contributing to approximately 10-15% of global female malignancy-related mortalities, with an annual incidence of around 100,000 new cases (57). A persistent infection with high-risk strains of human papillomavirus (HPV) is acknowledged as the primary predisposing factor for cervical cancer. In a comprehensive analysis of oncogenic human viruses, Hoppe-Seyler and Hoppe-Seyler (58) illuminated the potential role of lncRNAs in modulating the HPV-induced carcinogenic process, influencing the transcriptional regulation of target genes and proteins either positively or negatively and thereby determining the progression and eventual development of cervical cancer.

A seminal study conducted in 2012 by Gibb *et al* (59) employed serial analysis of gene expression to scrutinize 16 tissues exhibiting varying grades of cervical intraepithelial neoplasia (CIN). They discovered 1,056 lncRNAs with differential expression in CIN compared with healthy cervical tissues, making this the first time a differential lncRNA profile for CIN had been reported. Subsequent research unearthed 617 lncRNAs implicated primarily in metabolic and immunologic pathways associated with cervical cancer, including the p53 and cAMP signaling pathways. The researchers developed a prognostic signature based on eight lncRNAs (RUSC1-AS1, LINC01990, LINC01411, LINC02099, H19, LINC00452, ADPGK-AS1 and C1QTNF1-AS1) and revealed that the interaction among these lncRNAs correlated significantly with adverse prognosis in cervical cancer patients (60).

The role of lncRNA H19 in cervical cancer has been under investigation for approximately two decades. An early study in 2002 by Kim *et al* (61) and associates examined the relationship between imprinting regulatory deficiency and tumorigenesis at the epigenetic level in 32 cases of cervical

squamous cell carcinoma across different clinical stages. Their findings suggested that alterations in the expression levels of lncRNA H19 and IGF-2 were implicated in cervical cancer progression. In another study, Iempridee (62) demonstrated that lncRNA H19 expression was markedly elevated in cervical cancer cell lines, with both overexpression and knockdown experiments indicating that lncRNA H19 spurred cell proliferation and multicellular tumor sphere formation. However, this did not significantly effect cell apoptosis or migration. Subsequent research further elucidated the role of lncRNA H19 in cervical cancer, indicating a higher expression in cancerous compared with adjacent healthy tissues and a negative correlation with miR-138-5p expression. Furthermore, upregulation of miR-138-5p following lncRNA H19 knockdown with small interfering RNA (siRNA) in HeLa and SIHA cells was observed. SIRT1 was confirmed as a target of miR-138-5p in cervical cancer, with the latter inhibiting tumor formation via SIRT1. This suggested a possible mechanism by which lncRNA H19 might contribute to cervical cancer, potentially by acting as a sponge for miR-138-5p, thereby targeting SIRT1 (63) (Fig. 2).

The prognostic value of lncRNA H19 in cervical cancer has been previously appraised. The analysis of patient data with cervical cancer, featuring lncRNA H19 overexpression from The Cancer Genome Atlas database, was carried out using Kaplan-Meier survival curves and the Cox proportional hazard model. This analysis evaluated parameters such as the hazard ratio (HR), overall survival, disease-free survival, relapse-free survival, metastasis-free survival and progression-free survival. Results denoted lncRNA H19 as an independent prognostic indicator for cervical cancer (HR=4.099; P<0.05) (64).

lncRNA H19 and endometrial cancer. Endometrial cancer, representing the most prevalent gynecological malignancy in industrialized nations, has exhibited an alarming upward trajectory in incidence over recent years. This trend, particularly noticeable in North America and Eastern Europe, aligns with demographic shifts such as aging and increasing obesity rates. In 2018, the United States documented 63,230 new cases, alongside 11,350 mortalities, underscoring the gravity of this public health concern (65,66).

Endometrial cancer manifests predominantly in two subtypes. Type I, constituting 80-90% of incidences, typically afflicts premenopausal or postmenopausal women, frequently evidencing positivity for estrogen and progesterone receptors within tumor tissues and generally offering patients a favorable prognosis (67). By contrast, Type II emerges from postmenopausal atrophic endometrium and is often associated with a dismal prognosis (68). Utilizing resources like the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases, researchers have identified 172 differentially expressed lncRNAs in endometrial cancer tissues relative to the normal endometrium (69). However, rigorous investigations into the implications of these lncRNAs in endometrial cancer remain scarce. Available studies predominantly center on MALAT1, HOTAIR, lncRNA H19 and SRA (70). Intriguingly, the expression patterns of lncRNAs in endometrial cancer are subtype-specific; for instance, the ovarian carcinoma magnifying lncRNA is downregulated in type II and upregulated in type I endometrial cancer (71).

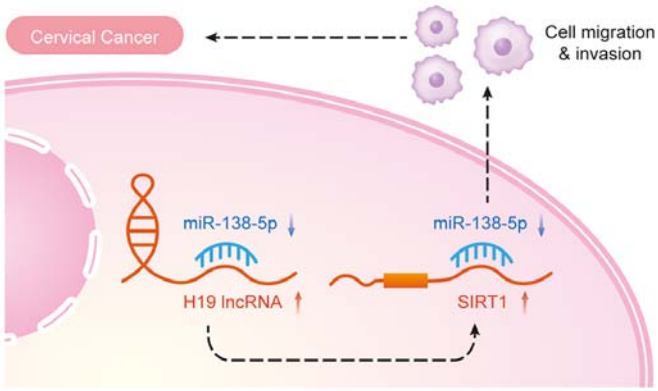

Figure 2. Role of lncRNA H19 in the pathogenesis of cervical cancer: Modulatory mechanism involving miR-138-5p and the targeting of SIRT1. lncRNA, long noncoding RNA; miR, microRNA; SIRT1, sirtuin 1.

In an earlier study conducted in 2004, Tanos *et al* (72) and colleagues examined lncRNA H19 and IGF-2 gene expressions in normal, hyperplastic and cancerous endometrial samples. They found an elevated frequency and level of lncRNA H19 in endometrial cancer, which correlated with the degree of differentiation, while IGF-2 expression remained consistent. In line with the mechanisms observed in other cancers, lncRNA H19 primarily exerts its biological influence through the lnc-miRNA axis and affects the EMT process. Zhang *et al* (73) revealed a significant upregulation of lncRNA H19 and Homeobox protein Hox-A10 (HOXA10), coupled with miR-612 downregulation, in endometrial cancer. Survival analysis suggested an inverse correlation between lncRNA H19 and patient survival rates. *In vitro* experiments confirmed that lncRNA H19 regulates cellular proliferation by competitively targeting HOXA10 via miR-612 in endometrial cancer, contributing to its pathogenesis (73).

Further research employing RT-PCR to determine the expression profile of lncRNA H19 in endometrial cancer revealed markedly elevated levels in tumor tissues compared with adjacent tissues. Knockdown experiments demonstrated that lncRNA H19 suppression curtailed the migratory and invasive potential of endometrial cancer cells without influencing cell growth. Concurrently, increased E-cadherin expression and unchanged vimentin levels indicated a partial EMT reversal, suggesting that lncRNA H19 modulates endometrial cancer cell invasion by regulating EMT (74) (Fig. 3).

Research conducted by Peng *et al* (64) and colleagues underlined the prognostic significance of lncRNA H19 in female malignancies, noting its overexpression correlates with poorer endometrial cancer prognosis. Given that diabetes and obesity represent risk factors for endometrial cancer, metformin (a common therapeutic intervention for type 2 diabetes) has been used in preventative and therapeutic strategies against malignancies, including endometrial cancer (75). The molecular underpinnings of its anticancer effects, however, remain elusive. Notably, Yan *et al* (76) demonstrated that metformin inhibited the migration and invasion of endometrial cancer cells by downregulating lncRNA H19 expression via DNA methylation. This compelling finding underlines a potential mechanistic rationale for the use of metformin in the prevention and treatment of endometrial cancer.

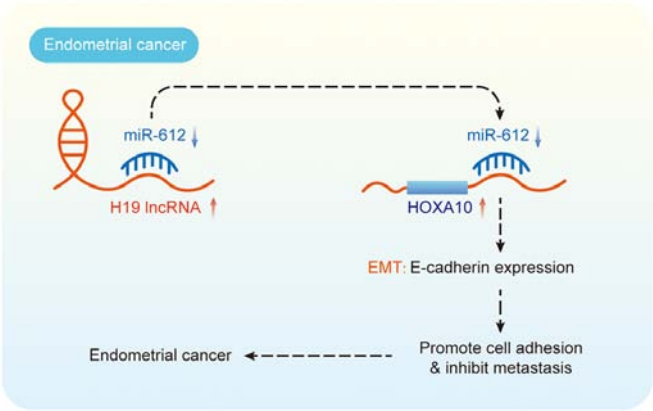

Figure 3. Contribution of lncRNA H19 to endometrial cancer pathogenesis via competitive interaction with mIR-612 and targeting of HOXA10. lncRNA, long noncoding RNA; miR, microRNA; HOXA10, Homeobox protein Hox-A10.

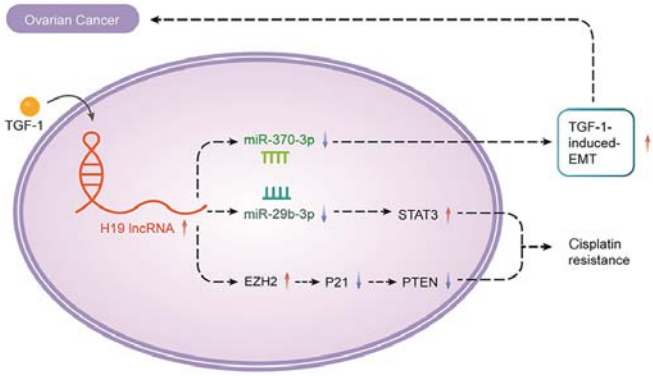

Figure 4. Function of lncRNA H19 as a ceRNA in the pathomechanism of ovarian cancer and chemotherapy resistance. lncRNA, long noncoding RNA; ceRNA, competitive endogenous RNA; miR, microRNA; TGF-1, transforming growth factor-1; EMT, epithelial-mesenchymal transition; EZH2, enhancer of zeste homolog 2.

lncRNA H19 and ovarian cancer. Ovarian cancer represents a principal source of mortality among gynecological malignancies, with diagnosis often occurring at advanced stages due to the paucity of efficacious detection methodologies. According to 2018 data, ovarian cancer engendered 22,240 new cases and led to 14, 070 mortalities in the United States alone (65). The application of GO and KEGG pathway analyses in discerning the lncRNA profile of 30 human ovarian carcinoma tissues in relation to 20 normal ovarian tissues has yielded salient results: 795 upregulated and 2,075 downregulated lncRNAs were detected in ovarian cancer tissues compared with their normal counterparts. The identified differentially expressed lncRNAs were categorized into four classes, namely, enhancer lncRNAs adjacent to coding genes, HOX cluster, long intergenic non-coding RNAs (lincRNAs) adjacent to coding genes and Rinn lincRNAs. This classification laid the groundwork for subsequent in-depth functional studies (77).

In high-grade serous ovarian cancer, a different study documented 1,511 upregulated and 2,778 downregulated lncRNAs associated with normal fallopian tube tissues, corroborating the upregulation of FAS-AS1, AK130076, RP11-199F11.2 and AC093818.1 and the downregulation of GTSE1-AS1 in ovarian cancer tissues (78). Noteworthy is the observed variation in the biological roles of lncRNAs across the various stages of ovarian cancer (79). Correlations were found between the expression level of lncRNAs and diagnostic time, prognosis and chemotherapy resistance (80). Furthermore, the involvement of estriol-regulated lncRNA and its polymorphic methylation in ovarian cancer was elucidated (81). Additionally, a total of 26 lncRNAs, comprising 5 upregulated and 21 downregulated, were flagged as potential multidrug-resistant lncRNAs based on data integration of published research and cisplatin-resistant lncRNAs in ovarian cancer cell lines or patients. Importantly, lncRNA CTD-2589M5.4 demonstrated coexpression with the multidrug resistance genes ABCB1, ABCB4, ABCC3 and ABCG2, thereby providing key insights into the roles of lncRNAs in the multidrug resistance process (81).

Scientific inquiry into the role of lncRNA H19 in ovarian malignancies began with explorations of the H19 and IGF-2 genes. An early study in 2000 by Chen *et al* (82) evaluated the imprinting status of the H19 gene and IGF-2 in a selection of ovarian cancer samples, ovarian tumors of low malignant potential and normal ovarian tissues. The results unveiled an imprinting deletion in all cases of advanced stage, hinting at a potential association between the H19 gene and IGF-2 imprinting deletion and advanced ovarian cancer. Subsequent research by Zhu *et al* (83) confirmed elevated expression of lncRNA H19 in ovarian cancer samples compared with normal ovarian tissue. Upon knockdown of lncRNA H19, cell cycle arrest was observed alongside aberrant expression of apoptosis-related proteins and inhibited proliferation in OV90 and SKOV3 ovarian cancer cell lines. Li *et al* (84) probed the mechanistic underpinnings of the involvement of lncRNA H19 in ovarian cancer and found that TGF-1 treatment led to an upregulation of lncRNA H19 and a downregulation of miR-370-3p. Moreover, H19 gene knockdown or miR-370-3p overexpression attenuated the TGF-1-induced EMT, while H19 overexpression or miR-370-3p gene knockdown facilitated this process. Consequently, this study affirmed the role of lncRNA H19 as a ceRNA sponging miR-370-3p, thereby influencing the promotion of TGF-1-induced EMT (Fig. 4).

Platinum-based chemotherapy represents a cornerstone of advanced ovarian cancer treatment, but the emergence of platinum resistance presents a significant impediment to successful therapeutic outcomes. The mechanism underlying the platinum resistance of ovarian cancer is complex, governed by a myriad of molecular entities. One study by Tian *et al* (85) discovered that lncRNA-H19 and STAT3 levels were significantly elevated, while miR-29b-3p levels were diminished, in carboplatin-resistant epithelial ovarian cancer. Furthermore, lncRNA-H19 functioned as a ceRNA of miR-29b-3p, instigating the derepression of the downstream miR-29b-3p target, STAT3 and consequently conferring chemoresistance. Importantly, silencing of lncRNA-H19 augmented carboplatin efficacy, suggesting a potential pathway for enhancing chemotherapy.

Ongoing efforts are underway to discover novel therapeutic strategies for patients exhibiting platinum resistance. Sajadpoor *et al* discerned that valproic acid (VPA), a prevalent antiepileptic drug, could mitigate ovarian cancer via lncRNA regulation (86). Post-VPA treatment, the cisplatin-resistant ovarian cancer cell line A2780-DR exhibited downregulated levels of lncRNA H19 and EZH2 and upregulated levels of

p21 and PTEN. Moreover, lncRNA H19 knockdown instigated apoptosis and revived the sensitivity of A2780/CP cells to cisplatin, intimating that VPA may attenuate lncRNA H19 in ovarian cancer and inhibit cisplatin resistance via the lncRNA H19/EZH2/p21/PTEN signaling pathway (86).

Ginsenoside, an active constituent of traditional Chinese medicine Panax ginseng, exerts antitumor effects via a multitude of intricate mechanisms. Zheng *et al* (87) revealed that the Warburg effect, a fundamental metabolic characteristic of malignant tumors, is modulated in part by lncRNAs. Ginsenoside 20 (S)-RG3 mitigated the competitive inhibitory effect of lncRNA H19 on miR-324-5p in ovarian cancer, enhancing the inhibitory effect of miR-324-5p on PKM2, thereby suppressing the Warburg effect and ultimately inhibiting tumorigenesis. This discovery provides a promising foundation for the therapeutic application of ginsenosides in ovarian cancer (87).

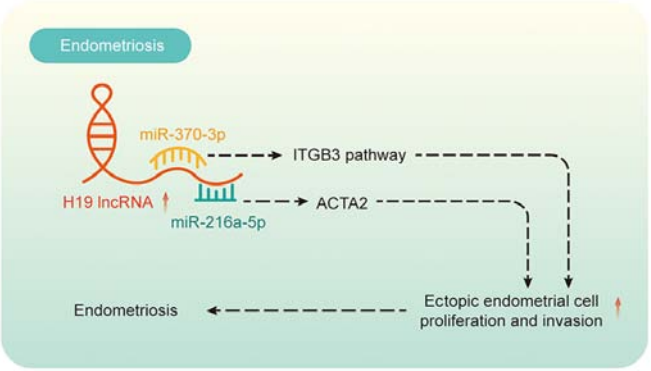

Figure 5. Regulatory pathway involving lncRNA H19, miR-124-3p and ITGB3 in modulating ectopic endometrial cell proliferation and invasion in endometriosis. lncRNA, long noncoding RNA; miR, microRNA; ITGB3, integrin β3; ACTA2, actin α2.

5. lncRNA H19 and benign gynecological diseases

lncRNA H19 and endometriosis. Endometriosis is pathologically characterized by the ectopic growth of active endometrial tissue beyond the confines of the uterine cavity, a condition that precipitates associated clinical symptoms. This disease, predominantly affecting 10-15% of women within their reproductive years, manifests as a benign disorder that paradoxically displays malignant biological tendencies, thereby detrimentally affecting women's physical and psychological wellbeing (88,89). The etiological underpinnings of endometriosis remain elusive, with an unmet need for robust biological markers capable of early-stage diagnosis and predicting disease recurrence. An examination of reports pertaining to ncRNAs and endometriosis, extracted from PubMed, MEDLINE and Google Scholar databases between 2000 and 2016, suggested that ncRNA regulatory dysregulation significantly contributes to endometriosis. Importantly, microRNAs, lncRNAs and siRNAs serve pivotal roles in endometriosis by modulating inflammatory processes, cellular proliferation, angiogenesis and tissue remodeling (90). The identification of ncRNA biomarkers relevant to endometriosis offers novel avenues for diagnostic methods and therapeutic targets, potentially revolutionizing clinical management for patients suffering from endometriosis (90).

Over recent years, the lncRNA expression profile in endometriosis has been elucidated (91-94). Notably, Cui *et al* (91) explored the differences in lncRNA expression between eutopic and normal endometrium during the proliferative phase, predicting potential lncRNA targets based on cis- and trans-regulatory actions. Additionally, they annotated the functions of coexpressed mRNAs, identifying a total of 9,924 novel ncRNA transcripts. Of these, 86 lncRNAs and 1,228 mRNAs demonstrated differential expression between endometriosis patients and controls. GO and KEGG analyses indicated these lncRNAs were significantly involved in the biological processes and signaling pathways characteristic of endometriosis. Wang *et al* (93) identified a total of 1,277 differentially expressed lncRNAs (comprising 488 upregulated and 789 downregulated lncRNAs) between the eutopic and normal endometrium in the late secretory phase. These lncRNAs interacted with 1,216 differentially expressed mRNAs in a coexpression network encompassing both coding and noncoding genes. Notably, upregulated lncRNAs were predominantly associated with cell cycle regulation, including DNA replication and cell cycle progression, while downregulated lncRNAs were linked to immune-related pathways, such as tumor necrosis factor (TNF), Wnt and mitogen-activated protein kinase (MAPK) signaling pathways. According to these findings, lncRNA expression profiles in endometriosis are subject to fluctuations across menstrual cycle phases. A study by Wang *et al* (94) further explored serum lncRNA levels in endometriosis patients, identifying 1,682 differentially expressed lncRNAs, with 125 lncRNAs concurrently detected in serum and tissue samples. Multiple reports have detailed the mechanisms through which lncRNAs contribute to endometriosis (95-98). For instance, actin filament associated protein 1 antisense RNA1 (AFAP1-AS1) has been demonstrated to promote EMT by modulating the transcription factor ZEB1 (95). Additionally, the lncRNA MALAT1 has been found to mediate the autophagy of endometrial stromal cells under hypoxic conditions (96). The long intergenic non-protein coding RNA01279 (lincRNA01279) has been implicated in endometriosis progression via regulation of the cell cycle (97).

lncRNA H19 represents the first lncRNA subjected to functional research within the context of endometriosis. In a prior investigation, the current authors identified that perturbations in the lncRNA H19/miR-124-3p/integrin β3 (ITGB3) pathway modulated ectopic endometrial cell proliferation and invasion in endometriosis (99). Another study found that lncRNA H19 regulated the invasion and migration of endometriosis eutopic endometrial stromal cells by modulating miR-216a-5p and actin α2 and that estrogen promoted eutopic endometrial stromal cell invasion and migration via lncRNA H19 (100) (Fig. 5). The current authors also examined the overexpression of lncRNA H19 in endometriosis and its potential as a novel biomarker for predicting disease recurrence. Their findings indicated that lncRNA H19 expression in ectopic endometrium correlated with infertility, disease recurrence, bilateral ovarian lesions, elevated CA125 levels and revised American Fertility Society stages. Moreover, the receiver operating characteristic curve analysis revealed that, when lncRNA H19 expression in ectopic endometrium exceeded 0.0277, the sensitivity and

specificity for predicting recurrence were 90.9 and 61.0% respectively, implying the potential involvement of lncRNA H19 in the pathogenesis of endometriosis and its potential utility as a novel predictor of disease recurrence (101).

The immune system serves a vital role in the pathophysiology of endometriosis, particularly Th17 cells, which are a subset of pro-inflammatory T-helper cells known to exacerbate the disease. According to a study of immune cells, lncRNA H19 and IER3 expressions were found to be downregulated in mononuclear cells from peritoneal fluid (PFMCs) of patients with endometriosis or under Th17 differentiation conditions (102). By contrast, miR-342-3p expression was up-regulated and the percentage of Th17 cells was increased in these PFMCs. The overexpression of lncRNA H19 decreased IL-17 level and the percentage of Th17 cells/CD4+ T cells, indicating that lncRNA H19 overexpression can suppress Th17 cell differentiation and endometrial stromal cell (ESC) proliferation through the miR-342-3p/IER3 pathway (102). A possible therapeutic approach could involve strategies to overexpress lncRNA H19 in PFMCs of patients with endometriosis. Overexpression of lncRNA H19 could be achieved using gene therapy techniques, such as the use of viral vectors to deliver the lncRNA H19 gene into target cells. However, these techniques would need to be carefully optimized to ensure targeted delivery and avoid off-target effects. Monitoring the efficacy of the treatment would be crucial. This could be done by tracking the expression levels of lncRNA H19, miR-342-3p and IER3, as well as the percentage of Th17 cells in the PFMCs of patients. Changes in these markers would provide valuable information about the biological effect of the therapy and its effect on the disease progression.

lncRNA H19 and infertility. Animal studies have revealed differential lncRNA profiles pre- and post-pregnancy, as well as across distinct stages of embryo implantation, pointing towards a critical role of lncRNAs in the regulation of embryo implantation (103,104). Inadequate endometrial receptivity constitutes the primary reason for failed pregnancies. In patients undergoing *in vitro* fertilization-embryo transfer with repeated implantation failure (RIF), the endometrial expression of lncRNAs and mRNAs revealed 1,202 differentially expressed genes compared with healthy endometrium, including 742 lncRNAs and 460 mRNAs. The implicated targets were primarily associated with tumor necrosis factor, Toll-like receptor and nuclear factor-kappa B (NF-κB) signaling pathways (105).

Huang *et al* (106) revealed a distinct lncRNA profile in the endometrium of patients with RIF compared with healthy counterparts, as determined by weighted gene coexpression network analysis, suggesting the potential involvement of lncRNAs in modulating endometrial receptivity. Building on this, Feng *et al* (107) constructed a lncRNA-mRNA network associated with implantation failure and identified six crucial lncRNAs and their ceRNA subnetwork through unsupervised clustering, GO, KEGG and coexpression module analyses. This revealed key biological processes such as immune activity, growth factor binding, vascular proliferation, apoptosis and steroid synthesis, suggesting that lncRNAs may work in concert to ensure endometrial receptivity for embryo implantation (107).

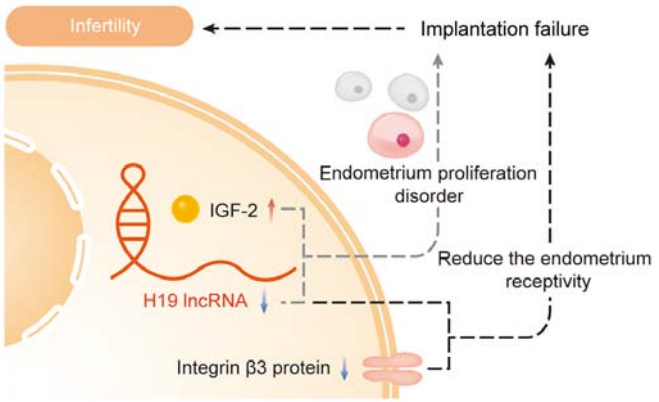

Figure 6. Influence of lncRNA H19 on endometrial receptivity: potential implications for infertility. lncRNA, long noncoding RNA; miR, microRNA; IGF2, insulin-like growth factor 2.

The H19 gene expression in the endometrium was found to be cyclical, fluctuating across the menstrual cycle (108). Early research demonstrated a decline in H19 expression with ovulation, which remained low until the early secretory phase, gradually increased on the 21st day of the cycle, reaching a peak and persisting until the end of the menstrual cycle (108). Furthermore, Korucuoglu *et al* (109) discovered that decreased H19 and increased IGF-2 expressions in the endometrium of unexplained infertility cases negatively affected endometrial proliferation, leading to implantation failure, thus proposing H19 as a potential biomarker or gene therapy target in assisted reproductive technologies (109). Zeng *et al* (110) reported decreased levels of lncRNA H19 and integrin β3 protein in the endometrium during the middle luteal phase in infertile patients with RIF compared with controls. They proposed that the downregulation of lncRNA H19 diminished integrin β3 protein expression, consequently reducing endometrial receptivity and causing implantation failure (Fig. 6).

Post-implantation, a proportion of pregnancies suffer loss during embryonic development, with the etiology largely undetermined. Existing literature posits an essential role for lncRNAs in embryogenesis and fetal growth (27,28), prompting investigations into the link between lncRNAs and spontaneous abortions. Wang *et al* (111) performed lncRNA profile analyses of blastocysts and decidua from 16 spontaneous abortion cases and 16 induced abortion cases, identifying differentially expressed lncRNAs implicated in six biological pathways, including infection and inflammation, metabolism, signal and transcription regulation, smooth muscle contraction, cell process and coagulation and infection and inflammation. The lncRNAs associated with these pathways were proposed as the key etiological factors for spontaneous abortions. In the embryonic chorion tissue from spontaneous abortion cases, lncRNA H19 was observed to regulate trophoblastic spheroid adhesion to endometrial stromal cells by targeting ITGB3 via let-7 modulation (112).

In a further study, Hu *et al* (113) evaluated the expression of lncRNA H19, miR-200 and ZEB1 in the chorionic tissues of 20 patients with spontaneous abortions and 20 women who had undergone induced abortions. The findings showed diminished lncRNA H19 and ZEB1 expressions in the spontaneous abortion group compared with the induced abortion

group, with moderate positive correlation between their levels. By contrast, there was no discernible difference in miR-200 expression across the two groups, suggesting the possible involvement of lncRNA H19 in spontaneous abortions via ZEB1 regulation.

Moreover, it was reported that the lncRNA H19 expression was notably lower in the spontaneous abortion group compared with the control group, with positive associations observed with Bcl-2 and GPX4 expressions and negative correlation with Bax expression. Furthermore, the silencing of lncRNA H19 was found to downregulate Bcl-2 and GPX4 expressions, but upregulated Bax expression in HTR-8/SVneo trophoblast cells. These observations suggest that lncRNA H19 may have significant roles in spontaneous abortions by facilitating apoptosis and ferroptosis (114).

6. Effects of lncRNA H19 on immunity

lncRNAs have gained significant attention for their wide-ranging roles in gene regulation, cellular functions and disease etiology. Among the multitude of lncRNAs under rigorous examination, lncRNA H19 stands out due to its multifaceted involvement in immune response modulation across various pathological contexts. In gastric cancer (GC), a highly prevalent malignancy, lncRNA H19 has been found to regulate immune cell infiltration via miR-378a-5p/SERPINH1 signaling (115). This mechanism is believed to contribute significantly to GC progression, highlighting the dynamic interaction between H19 and immune cells. Moreover, lncRNA H19 has been implicated in the regulation of aerobic glycolysis and cell proliferation, serving an instrumental role in immune evasion in GC cells via the miR-519d-3p/lactate dehydrogenase A axis (48). Markedly, research has indicated that knocking down H19 can reduce the immunosuppressive effect of GC cells, suggesting a promising therapeutic avenue (48). Further emphasizing the immune-related effects of lncRNA H19 is its role in thyroid carcinoma (THCA). lncRNA H19 has been found to be differentially expressed in THCA, with its expression associated with immune cell infiltration in the disease. Specifically, it was found to be positively correlated with the infiltration level of various immune cells such as CD4+ T cells, CD8+ T cells, B cells, dendritic cells, neutrophils and macrophages. Moreover, lncRNA H19 was associated with multiple immune markers, underscoring its potential role in shaping the immune landscape of THCA (116).

In the context of systemic lupus erythematosus (SLE), an autoimmune disease, lncRNA H19 exhibits a significant upregulation and is associated with immune dysregulation in bone marrow-derived mesenchymal stem cells (BMMSCs) (117). The mechanism, notably, involves H19 inhibiting the production of the interleukin-2 cytokine, an important modulator of immune responses. This finding not only broadens the known landscape of lncRNA H19-mediated immunomodulation but also positions H19 as a potential therapeutic target for SLE. Beyond its association with cancer and autoimmune disease, lncRNA H19 also serves a critical role in mammary epithelial cells. Overexpression of lncRNA H19 promotes cell proliferation and enhances the expression of proteins related to cell structure and function, such as β-casein and tight junction-related proteins (118). Furthermore, it influences immune responses by increasing the expression of inflammatory factors [TNF-α, interleukin 6, chemokine (C-X-C motif) ligand 2 and chemokine (C-C motif) ligand 5] and activating the NF-κB signal pathway, thus potentially linking H19 to inflammatory disorders of the breast, including mastitis and possibly even breast cancer (118,119).

Overall, the effect of lncRNA H19 on immune regulation is diverse and context-dependent, with its involvement in a wide range of diseases and cellular functions. A recurring theme in the literature is the relationship between lncRNA H19 and inflammatory responses. lncRNA H19 has been associated with heightened inflammation, frequently observed in diseases such as endometriosis and ovarian cancer, probably by modulating immune response genes and regulating cytokine production. The upregulation of lncRNA H19 perpetuates an inflammatory microenvironment, favoring disease progression through several mechanisms including promoting cytokine production, fostering immune cell recruitment and proliferation and enhancing expression of inflammatory genes (120). The potential value of lncRNA H19 as a therapeutic target to dampen excessive inflammation, offering potential treatment avenues for inflammatory gynecological conditions.

The effect of H19 on the immune response and gynecological diseases does not exist in isolation. The intricate network of microRNAs, epigenetic modifications and signal transduction pathways form a convoluted regulatory network with H19 at the center (121,122). The functionality of this network depends on a delicate balance, the disturbance of which can lead to pathological states (37,120). Consequently, a comprehensive understanding of these interactions is key for the development of effective therapeutic strategies targeting lncRNA H19 (37). However, despite the wealth of evidence linking lncRNA H19 with immune regulation, the precise mechanisms through which lncRNA H19 exerts its effects remain to be elucidated. The inherent complexities of lncRNAs, combined with the multifaceted nature of immune responses, present challenges to fully elucidating the roles of H19 in gynecological disease pathogenesis (123). Future studies, perhaps employing advanced techniques such as single-cell RNA sequencing and high-throughput chromatin conformation capture, could aid in painting a more comprehensive picture of H19's functional role in these diseases.

7. Conclusion

In summary, the lncRNA H19 has been discerned to serve a critical role in the etiology of diverse benign and malignant pathologies in gynecological health, employing a multiplicity of mechanisms. This molecular entity holds promise as an efficacious biomarker for early-stage detection and prognostic assessment of gynecological conditions, while also potentially offering a novel avenue for therapeutic intervention. However, the existing body of research concerning lncRNA H19 in the realm of gynecology is still in its nascent stage and the intricate role that H19 serves in disease initiation, advancement and modulation of the immune milieu in gynecology remains predominantly elusive.

Therefore, it is imperative that the labyrinthine regulatory network of lncRNA H19 be further elucidated, particularly in the context of its influence on various gynecological diseases.

Advancements in cellular and molecular biology, coupled with cutting-edge gene technology, pave the way for this endeavor. Moreover, the execution of additional clinical and fundamental experiments, utilizing larger sample sizes, will augment our understanding of the functionality and mechanistic underpinnings of lncRNA H19 in gynecological diseases. In turn, this acquired knowledge can expedite the evolution of diagnostic procedures and therapeutic strategies in gynecology, thereby elevating patient care standards.

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Availability of data and materials

Not applicable.

Authors' contributions

WX conceived the idea for the present study and drafted and revised the manuscript. YW and SL contributed to the revision, the provision of some of the data and databases, and also contributed to the proofreading and language correction of the manuscript. WX and KH performed the literature search and prepared the figures. YW and SL critically discussed and revised the manuscript, and provided some updates on the literature and clinical trials. All authors read and approved the final manuscript. Data sharing is not applicable to this article.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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