



Review

Deciphering the role of circulating miRNAs in the etiology and pathophysiology of endometriosis: An updated compiled review

Anuja Pant^a, Kareena Moar^a, Taruna K. Arora^b, Tikam Chand Dakal^c, Vipin Ranga^d,
Narendra Kumar Sharma^e, Pawan Kumar Maurya^{a,*}

^a Department of Biochemistry, Central University of Haryana, Mahendergarh, India, 123031

^b Reproductive Biology and Maternal Child Health Division, Indian Council of Medical Research, New Delhi, 110029, India

^c Genome and Computational Biology Lab, Department of Biotechnology, Mohanlal Sukhadia University, Udaipur, 313001, Rajasthan, India

^d DBT-NECAB, Assam Agricultural University, Jorhat, 785013, Assam, India

^e Department of Bioscience and Biotechnology, Banasthali Vidyapith, Tonk, 304022, Rajasthan, India

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ABSTRACT

Endometriosis is characterized by the presence of endometrial tissue outside of the uterus. It is a benign chronic condition with incapacitating symptoms like infertility and pelvic pain. Endometriosis has a detrimental impact on the reproductive health of women, placing a heavy financial strain on the medical system. It is a multifactorial disorder governed by numerous mechanisms or risk factors that contribute to the pathologies of the disease. With limitations in diagnostics techniques, it is challenging to detect the disease at an initial stage. In around 1 % of endometriotic patients malignant state may reach, leading to severe consequences. To overcome such challenges, at present, numerous circulating miRNAs have been studied in plasma or serum samples from patients with endometriosis to develop a non-invasive diagnostic biomarker-based tool to identify the disease early. Our review compiles the miRNAs in bodily fluids that are linked with endometriosis-related mechanisms, which may serve as a potential biomarker. Some of these mechanisms are common in both cancer and endometriosis. Additionally, we have also emphasised the miRNAs with a putative role in cancer development and progression that could be used as a biomarker. This may further aid in protecting the 1 % of affected females from ovarian, breast, and in some cases endometrial cancer. We have come across several miRNAs associated with multiple mechanisms associated with endometriosis. miR-199a and miRNAs-let-7 family are some of the most common miRNAs that assist in multiple mechanisms such as cell proliferation, invasion, apoptosis, and epithelial-mesenchymal transition. Strategic planning and additional investigation into the identified miRNAs would make them a viable therapeutic target for the optimal management of endometriosis.

1. Introduction

Millions of women worldwide suffer from endometriosis, a devastating gynecologic disease that causes infertility, dysmenorrhea, and persistent pelvic discomfort. Endometriosis is marked by the growth of endometrial tissue outside the uterus [1]. It is a progressive disease that causes the formation of endometrial cysts in places such as ovaries, peritoneal cavity or other organs. The development of endometrial implants is estrogen-dependent. The aberrant aromatase activity owes to the local production of excess estrogen. Endometriotic lesions and associated symptoms may be lessened by hormonal treatments that inhibit the synthesis of estrogen [2,3]. Numerous theories attempt to

explain the cause of the disease. However, no single explanation can satisfactorily validate every facet of the pathophysiology of endometriosis. It is thought that a variety of anomalies in immunological, inflammatory, hormonal, genetic, and environmental variables combine to cause endometriosis [4,5]. Sampson proposed the theory of retrograde menstruation, which postulates that endometriotic cells return through the fallopian tube and spread throughout the peritoneal cavity. Sampson's idea raises a significant challenge because 90 % of menstrual women with normal fallopian tubes experience retrograde menstruation [6]. Women affected with endometriosis are more susceptible to autoimmune disorders, breast and ovarian cancer, and other malignancies than the general female population [7]. The gold standard to validate

* Corresponding author. Department of Biochemistry, Central University of Haryana, Mahendergarh, India.

E-mail address: pkmaurya@cuh.ac.in (P.K. Maurya).

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endometriosis is laparoscopy. This limits the early diagnosis of endometriosis due to the invasive approach [8]. Reproductive damage in women with endometriosis, especially mild form without anatomical aberrations due to adhesion, has been linked to mechanisms like altered folliculogenesis, higher oxidative stress, and low receptivity of the endometrium [9]. However, these explanations have not yet been experimentally validated [10]. Additionally, numerous components, that have been thoroughly researched, such as hormones (estrogen, progesterone), cytokines, glycoproteins, factors associated with angiogenesis, cytoskeleton molecules, oxidative stress markers, tumor markers, etc., cannot successfully identify the disease on their own or in isolation. Since early menarche is associated with a higher incidence of endometriosis in young females, it is critical to discover diagnostic biomarkers to enable early diagnosis and treatment in affected individuals [11]. A less intrusive diagnosis of endometriosis may depend on low-invasive testing such as genetic testing, imaging, biomarkers, or microRNAs (miRNAs) [12]. miRNAs play a vital role in regulating the expression of genes in plants and animals. These small molecules are non-coding, single-stranded RNAs consisting of approximately 22 nucleotides each. By binding to explicit messenger RNA (mRNA), miRNAs can trigger gene silencing through the degradation of mRNA or translational inhibition. Interestingly, miRNAs are known for their high stability, and they can be found both intracellularly and in circulation. It is possible to isolate miRNAs from several biological samples, including tissues, cells, and bodily fluids [13]. miRNAs are being investigated for medical screening and potential therapeutic targets since they have been connected to numerous human disorders.

The primary goal of this review is to provide future research directions and an overview of the putative role of various miRNAs utilized as non-invasive diagnostic biomarkers for endometriosis. miRNAs having a significant involvement in various regulatory mechanisms including cell differentiation, proliferation, apoptosis, tumorigenesis, and cell cycle have also been compiled. These mechanisms positively correlate with the development of endometriosis. Moreover, recent research has suggested the association of endometriosis with certain cancer types. Dysregulated expression of certain miRNAs is also reported in cancer initiation and progression in patients with endometriosis-associated cancer types such as EAO (Endometriosis-associated ovarian cancer). Therefore, exploring the expression profile of such miRNAs may be of use in endometriosis as well. Hence, the miRNAs involved in the regulation of these mechanisms may be associated with the disease and can be used for diagnosis and therapeutic intervention.

A literature review was conducted for this paper using databases PubMed, Science direct, Web of Science, and Google Scholar. Inclusion criteria include papers published between 2002 and 2024. Although papers from the last 20 years were given more emphasis. Any relevant papers of significance before that were also considered. Articles included in the literature review were filtered for miRNAs in diagnosis and therapeutics for the disease. Keywords included: Endometriosis, miRNA, Retrograde Menstruation, Laparoscopy, and Endometriosis Biomarkers. Papers published in language other than English were excluded from the review. Summaries of editorials, conferences, events, and papers published before 2002 were among the exclusion criteria. About 150 papers, including literature reviews, systemic reviews, research papers, comparative studies, and cohort studies, were studied in reviewing this work. Approximately 128 of these papers relevant to our study aim have been cited.

2. miRNA biogenesis

miRNAs are key regulators of mechanisms that aid in the progression of various diseases and are usually tissue-specific or circulating in nature. The circulating miRNAs are released into various biofluids such as blood, urine, saliva, seminal fluid, and breast milk. These releases can occur due to many mechanisms such as tissue injury, necrosis, apoptosis, microvesicles, and exosomes [14]. Hairpin-containing primary miRNA

transcripts, or pri-miRNAs, are the result of the transcription of miRNAs from genomic DNA by RNA polymerase II or III [15]. The RNase III enzyme Drosha and its cofactor DGCR8 (DiGeorge syndrome Critical Region 8) comprise the microprocessor complex, which transforms prim-miRNAs into precursor miRNAs (pre-miRNAs) in the nucleus [16]. These pre-miRNAs are processed by Dicer, another RNase III enzyme. Exportin-5 transports them to the cytoplasm, where they are transformed into double-standard miRNA duplexes. The RNA-induced silencing complex (RISC) is then formed by combining these duplexes. One duplex strand known as the mature miRNA is recruited for loading in the RISC. By base pairing with complementary sequences, these mature miRNAs subsequently direct the RISC to target messenger RNAs (mRNAs), which are primarily found in the 3' untranslated region (UTR) [17]. One of the crucial RISC protein constituents, argonaute, aids in mRNA degradation, controlling the activation or repression of genes. These duplexes are then incorporated into the RNA-induced silencing complex (RISC) Fig. 1 [18]. Recent studies on differential miRNA expression profiles have been of significance in the diagnosis of numerous diseases including endometriosis and other reproductive disorders.

3. Potential role of different Circulating-miRNAs in endometriosis-associated pathologies

Circulating miRNAs (cir-miRNAs) play an important role in rapid alterations of the menstrual cycle at the endometrial levels [19]. Numerous findings suggest that these miRNAs are known to regulate oxidative stress, inflammation, initiation & progression of cancer in 1 % of cases where endometriosis turns into a malignant state, epithelial-mesenchymal transition (EMT), metastasis, angiogenesis, estrogen signaling, and other mechanisms that are also associated with endometriosis.

3.1. Oxidative stress (OS)

The imbalance between reactive oxygen species and antioxidants results in oxidative stress which causes an inflammatory response in the peritoneal cavity. Reports suggest that microRNA networks and oxidative stress are closely interconnected in endometriosis and cancer-related biological processes [20]. Moreover, the amplified amount of Reactive Oxygen Species (ROS) produced is linked to higher rates of cell proliferation in both tumor and endometriotic cells. Endometriosis and ROS production are known to be related, and this relationship has been extensively researched [21,22]. Oxidative stress impacts the expression levels of several microRNAs, whereas microRNAs, in turn, influence numerous genes that are involved in responding to oxidative stress. Reports suggest that oxidative stress due to the build-up of certain cytokines such as interleukin-1 β , TNF- α , and β causes an upregulation of miRNAs-302a [23]. The major modulator of hypoxia, Hypoxia-Inducible Factor 1a (HIF-1a), is expressed when endometriosis has elevated ROS levels. It is known that high HIF-1a levels upregulate miR-20a, which is essential for maintaining angiogenesis in a hypoxic environment and allowing ectopic lesions to persist [24]. Endometriosis cell growth and inflammation may potentially be influenced by oxidative stress. The peritoneal fluid of endometriotic patients has been found to contain high amounts of ROS. Research indicates that increased ROS levels in cells have been shown to stimulate angiogenesis, degrade extracellular matrix, and trigger the production of proinflammatory cytokines through NF- κ B activation [25]. Studies have proven the protective role of miR-210-3p, which prevents the endometriotic cells from OS [26]. Oxidative stress and microRNA regulatory networks have an impact on various processes associated with inflammation, EMT, metastasis, angiogenesis and cancer-related signaling pathways [27,28]. These processes ultimately result in the superfluous expression of oncogenes leading to uncontrolled cell growth. Adjusting the amounts of a limited number of microRNAs can potentially reduce pathological oxidative

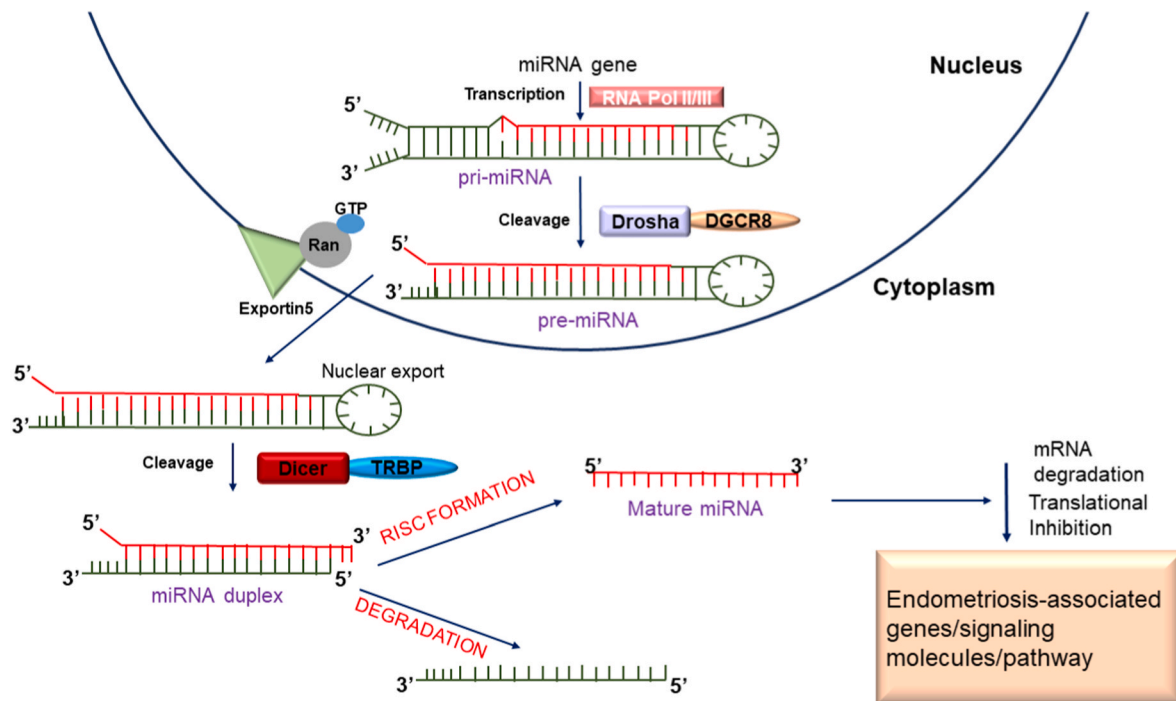


Fig. 1. Illustrates miRNA biogenesis with mature miRNA formed that regulates the endometriosis-associated mechanisms.

damage and offer chemo-preventive effects.

3.2. Inflammation

Inflammation is one of the most intricate molecular processes owing to the disease. Studies suggest that miRNAs are associated with inflammation in the context of endometriosis. Dysregulated miRNAs significantly influence the inflammatory pathways involved in the advancement of endometriosis. Studies demonstrate an increase in expression of serum-based miR125b-5p in patients with endometriosis known to be correlated with enhanced production IL-6 and TNF- α involved in proinflammation [25]. Serum levels of let-7b-5p are down-regulated due to an increase in TNF- α , IL-1 β , IL-6, and IL-8 leading to inflammation [29]. miR-146b isolated from the peritoneal fluid is also responsible for causing inflammation by reducing *IRF5* levels in endometriotic patients and plays a crucial role in endometriotic pain symptoms [30]. Findings suggest that patients experiencing pain symptoms often show elevated levels of miR-146b, which negatively regulates inflammation [31]. A study conducted in Hans Chinese women with moderate to severe endometriosis showed significantly reduced plasma miR-20a (Sensitivity: 60 %; Specificity: 90 %), miR-17-5p (Sensitivity: 60 %; Specificity: 80 %), and miR-22 (Sensitivity: 90 %; Specificity: 90 %) facilitating post-transcriptional inhibition of their up-regulated mRNA targets [32]. Moreover, decreased expression of miR-17-5p/20a supports the local inflammation milieu during lesion formation by targeting IL-8 and TNF- β [33]. It has been demonstrated that miR-155 contributes to compromised B, T, and dendritic cell growth and function. Signaling molecules that stimulate inflammation cause an increase in miR-155 expression in cancer cells. The immune response modulator *SHIP1* is downregulated by miR-155 [34]. Reports suggest that miR-155 also controls the expression of IL-12 in dendritic cells. Additionally, in mice with endometrial cancer, miR-155 inhibitors promoted the development of Th1 cells suggesting that miR-155 suppressed the expression of the p38 gene and decreased their ability to interfere in tumor development [35]. miR-155 in combination with other miRNA markers (miR574-3p, mir-139-3p) shows the sensitivity of 83 % in demonstrating a potential diagnostic marker of endometriosis [32].

3.3. EMT, cell proliferation, migration, invasion, and adhesion

The intricate interplay between the mechanisms, such as proliferation, cell adhesion, migration, invasion, and epithelial-to-mesenchymal transition, facilitates the growth and expansion of endometriotic implants at the ectopic site. The dysregulation of numerous molecular pathways, such as TGF- β and Wnt/ β -catenin impede detachment of endometrial epithelial cells from the uterine lining. These cells further migrate to the surrounding tissue, acquiring mesenchymal traits, resulting in the formation of endometrial lesions [36]. The loss of cell-cell communication at the eutopic site, followed by their contact development in the ectopic tissue, promotes the development and persistence of the endometriotic lesions. Dysregulated expression of adhesion molecules facilitates adhesion of the endometrial cells to the peritoneum [37]. Cell proliferation also plays a pivotal role in the pathogenicity of endometriosis. The endometrial cells exhibit enhanced proliferative capacity outside the uterus contributing to the development of endometrial-like tissue [38]. Several miRNAs have been studied that significantly impact these mechanisms and may be used as a biomarker in the prognosis of endometriosis. Contrarily, miR-29a-3p inhibits or attenuates the proliferation and migration of tumor cells of various subtypes of cancer, such as gastric cancer, cervical cancer, and endometrial cancer (EC). In EC, miR-29a-3p targets the VEGFA/CDC42/PAK1 signaling pathway and may be used as a valuable candidate for target treatment [39]. Investigation indicates that miR-29a-3p, miR-28-5p, and miR125b-5p in conjugation shown an acceptable sensitivity of 78 % [40]. Although miR-29a-5p discriminates between endometriotic patients with stage I and stage II and those without endometriosis, it exhibits a specificity of 37 % only. The metastasis of breast cancer cells is restricted by reduced expression of miR-28-5p, so it functions as a tumor suppressor [41]. In esophageal cancer, miR-28-5p stimulates cell proliferation leading to tumor development by reducing the expression of *MTSS1* [42]. Moreover, miR-199a ($p < 0.05$) shows a significant increase in the expression levels in patients with endometriosis compared to control. Studies highlight that miR-199a is strongly linked with the location of adhesion and dissemination of lesions [43]. The relative expression of miR-145 decreases significantly in patients with endometriosis with a sensitivity of 85 %

whereas among the patients with stage I and stage II endometriosis the sensitivity of 93.75 % and specificity of 50.79 % has been observed compared to control [44]. Among the miR-145 family, miR-145-5p regulates cell proliferation and migration by modulating different signaling pathways such as SOX2, KLF5, TAGLN2 [45]. Studies highlight significant downregulation of let-7b and miR-135a in endometriotic patients compared to control. Other miRNAs of the let-7 family, such as let-7d and let-7f, however, showed a tendency towards down-regulation. They also showed the highest area under the curve value (0.929) during the proliferative phase differentiating endometriotic patients from controls [46]. The plasma samples of patients with endometriosis show relatively higher levels of miR-33a-5p and significantly low levels of miR-196b-5p, miR-378a-3p, and miR-154-5p compared to controls. Studies highlight the importance of miR-154-5p in distinguishing endometriotic patients with control. miR-154-5p has been reported as a potential marker in endometrial carcinosarcomas where it participates in epithelial-mesenchymal transition [47]. The expression level of these miRNAs is governed by the phase of the menstrual cycle [48]. miR-326 has been reported as a promising biomarker for cancer and participates in cell invasion, tumor growth, and development [49]. Additionally, miR-326 and miR-485-3p are downregulated in both serum and plasma samples of women with endometriosis and proliferative versus secretory phases of the menstrual cycle in healthy women. Reports suggest that these miRNAs explicitly exhibit phase-dependent regulation of the cycle [50]. Constant downregulation of miR-196b has been reported in plasma samples of endometriotic patients. miR-196b negatively regulates the process of ectopic lesion implantation and formation [51] Fig. 2.

All these processes are also known to be associated with the development of endometriosis.

3.4. Metastasis

Sampson proposed the notion of metastatic endometriosis which suggested that an insignificant amount of endometrial tissue may spread through the lymph veins that drain the uterus during menstruation. The presence of capillaries in practically all organs explains well the theory of benign metastasis explaining the prevalence of endometriosis in

lymphatic nodes and remote places like the lungs [52]. At later stages of endometriosis, ectopic endometrial cells gain malignant properties. Certain miRNAs may help in detecting the transition from benign to malignant cysts. All the miRNAs outlined above concerning various mechanisms such as invasion, EMT, and migration have been known to be involved in metastasis as well.

miRNA-mediated regulation of cancer metastasis was first reported in 2007. These miRNAs were identified by comparing miRNA expression levels between normal human mammary epithelial cells, metastatic breast cancer cells, and non-metastatic breast cancer cells [53]. They found that the invasiveness of breast cancer cells into the lungs was positively correlated with the expression of miR-10b. Subsequently, the same research group in another study reported that silencing of miR-10b resulted in the inhibition of lung metastasis in mice bearing mammary tumors [54]. This highly studied miRNA plays an essential role in tumor cell migration, invasion, and metastasis, suggesting it to be a promising target for breast and glioblastoma therapy [55]. In another study, downregulated levels of ZNF652 have been reported in the promotion of breast cancer cell invasion and metastasis [56]. This gene is mainly regulated by the upregulated oncogenic miRNA, miR-155, which showed a positive correlation with local invasion in breast cancer cells [56]. Upregulated levels of miR-181 in breast cancer, gastric cancer, and prostate cancer are associated with vascular invasion and poor survival [57]. In this regulatory mechanism, the upregulated miR-181 promotes cancer cell proliferation by targeting SPRY4 in breast cancer and DAX1 in prostate cancer cells. Similarly, a cluster of highly homologous miR-221/222 was found overexpressed in breast cancer, pancreatic cancer, and hepatocellular cancer [58]. However, the correlation between its expression and tumor prognosis is still controversial due to its low levels of expression in prostate cancer and tongue squamous cell carcinoma. Thus, these examples demonstrate the potential of miRNAs as therapeutic targets in cancer treatment.

3.5. Cancer initiation and progression

Research indicates that women with endometriosis are marginally more likely to acquire specific forms of malignancies compared to women without the condition [59]. Although, the chances of conversion

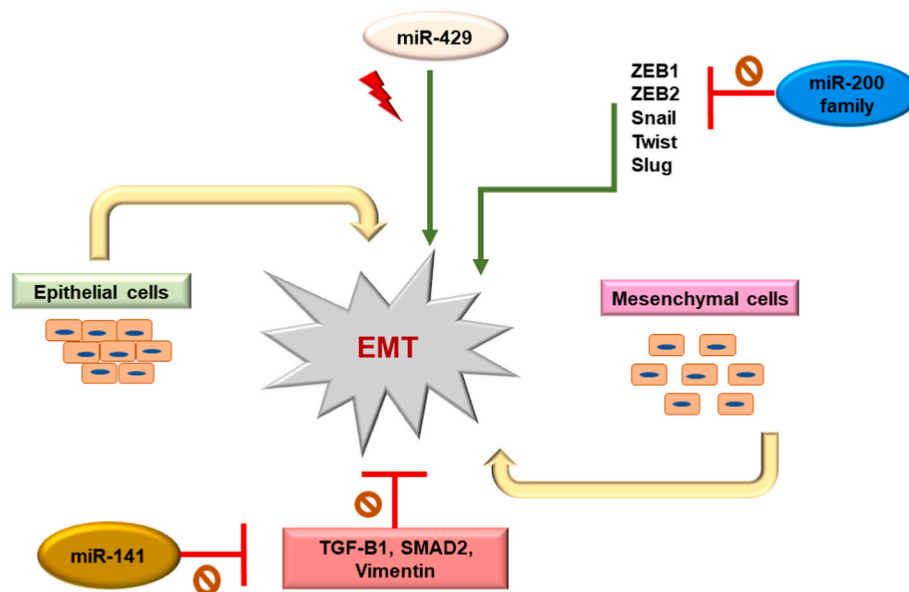


Fig. 2. The miR-200 family regulates epithelial-to-mesenchymal transition (EMT). The miR-200 family of miRNAs consists of five evolutionary conserved members, namely, miR-200a, miR-200b, miR-429, miR-200c, and miR-141. Members of the miR-200 family suppress important elements that drive epidermal migration. Several double-negative feedback loops regulating EMT plasticity are centred on the miR-200 family: one is direct and involves the transcription factors ZEB and SNAIL, while the other is indirect and involves signalling pathways that regulate ZEB and SNAIL. ZEB: Zinc finger E-box binding homeobox; SMAD2: Suppressor of mother against decapentaplegic; TGF-B1: Transforming Growth Factor-beta 1.

are very rare (~1 %) but may result in severe complications. Moreover, the latency in the diagnosis of women with endometriosis leads to severe complications. Till the time the woman is diagnosed with endometriosis, they already reached stages III and IV after which it acquires malignant properties. Several studies suggest the putative role of numerous miRNAs associated with endometriosis-related different cancer types [60]. Hence, investigating miRNAs involved in endometriosis-associated cancer may help in the prognosis of the disease by knowing their expression profile and association with the disease. Distinctive miRNA aberration has been linked to the onset, rapid growth, infiltration, and spread of different cancers [61]. Gaining knowledge of the functional activities of these miRNAs offers an essential understanding of the complex biological mechanisms that drive the progression of endometriosis-related cancers such as breast cancer [62], endometrial cancer (EC) [63], and ovarian cancer [64]. miRNAs are used as potential indicators for early diagnosis, stage-specific biomarkers, and targets for therapy [61]. Moreover, the capacity of certain miRNAs to function as prognostic markers and predictors of therapy response underscores their potential clinical usefulness in directing tailored therapeutic approaches [65]. Tan and co-authors (2022) analyzed regular clinical tissue samples of both benign and malignant lipomatous tumors, along with various sarcoma mimics [66]. The goal was to examine miRNA expression patterns that could serve as a supplementary method for identifying both benign and malignant adipocytic tumors. Several miRNAs are linked to gastric, prostate, pancreatic, lung, and other cancers [67–70]. Dakal and co-authors investigated the miRNA-gene regulatory networks and their significance in endometrial cancer [19]. Their work focuses on elucidating the intricate network of gene expression control and the role of microRNAs in the field of personalized medicine. miRNAs modulate tumor growth and metastasis via interacting with target genes within cells. MiRNA in colorectal cancer modulates the expression of tumor-specific markers, which exhibit both oncogenic and tumor-suppressive properties, similar to other forms of cancer [71,72]. Researchers have discovered a correlation between elevated serum miR-155 levels with endometrial cancer stage [73]. Researchers have found a link between endometriosis and a higher chance of getting ovarian cancer, specifically endometrioid and clear-cell ovarian cancer [74]. Studies have reported the involvement of miR-486-5p ovarian cancer associated with endometriosis. Serum levels of miR-486-5p were upregulated in patients with endometriosis-associated ovarian cancer compared to patients with only ovarian endometriosis [75]. These findings suggest that at later stages of endometriosis, most likely by stage IV, there is an enhanced increase in miR-486-5p levels. The increased expression of miR-486-5p considerably leads to proliferation of cell, migration and vice-versa. Torres et al. demonstrated that miR-223, miR-204, miR-186, and miR-222 in combination project better diagnostic biomarkers of endometriosis associated cancers [76,77]. MicroRNAs have the potential to improve the precision and potency of EC treatments due to their distinct qualities and shown efficiency. Therefore, examining the expression levels of these miRNAs at earlier stages of endometriosis may be of potential use before occurrence of severe complications.

3.6. Angiogenesis

Angiogenesis is marked by the formation of new blood vessels. In endometriosis the ectopic implant grows and functions outside the endometrium, which is regulated by some angiogenic factors. The finding suggests that during the progression of the tumor, angiogenesis stimulates the release of proangiogenic factors thereby stimulating tumor growth and metastasis [78]. The dysregulated expression of miR-130a, miR-27b and miR-210 in serum samples has been observed. The increased expression of these miRNAs plays a role in modulating processes such as angiogenesis and endothelial functions in patients having arteriosclerosis obliterans [79]. Although there is no evidence to support their role in endometriosis, it may be used as a putative

biomarker due to their involvement in the associated mechanisms. Serum levels of miR-199a have a significant impact ($p < 0.05$) in patients with endometriosis. Reports suggest that increased levels of miR-199a can be used as a potential diagnostic biosignature to distinguish between stage I and stage IV endometriosis. miR-199a expression is elevated in hypoxic environments. miR-199a decreases the angiogenic capacity of endometrial stem cells by blocking the HIF-1 α /VEGF-A pathway [80]. Higher expression of hsa-miR-33a-5p in the plasma of endometriotic patients compared to control suggests their role in the pathophysiology of the disease. Studies highlight the complicity of miR-33a-5p in regulating angiogenesis and vascularization under hypoxic conditions [81]. In colorectal cancer, miR-145-5p plays an essential role by inhibiting the process of angiogenesis and may be employed as a prospective biomarker for endometriosis as well [45].

3.7. Estrogen signaling and progesterone resistance

Endometriosis is an estrogen-dependent chronic disorder [82]. High production of estrogen, their receptors and progesterone resistance has been seen in patients with endometriosis. 17 β -estradiol, mostly produced locally, is essential for the maintenance of endometriotic tissue [83]. E2 binding to estrogen receptors (ER) leads to their activation and proper functioning. The hormone-mediated signaling pathways and various reproductive disorders such as endometriosis are closely linked. Endometriosis is marked by the local buildup of estrogen, which is transported into the bloodstream, having a substantial influence on the onset of endometrial lesions [84]. The impaired expression serum profile of miR-199a is associated with endometriosis which has been shown to engage in hormone-mediated signaling [43]. Previous research demonstrates a significant downregulation of serum miR-let-7b in endometriosis. Findings suggest that the let-7 family is closely related to the biosynthesis of estrogen [85]. Cells treated with an aromatase inhibitor show increased levels of let-7 suggesting the involvement of let-7b in the formation of endometriotic lesions [86]. Findings suggest that miR-9 (sensitivity: 66.7 %; specificity: 64.6 %) miR-145, and miR-141 ($p < 0.05$) serum expression significantly upregulates in samples of endometriotic patients with ovarian involvement compared to patients without ovarian endometrioma [44].

In normal endometrial tissue, progesterone aids in the transition from proliferative to the secretory phase. It exhibits anti-estrogenic characteristics and helps in maintaining the endometrium during pregnancy, expansion of the uterus, and implantation [87]. The downstream signaling is balanced through precise feedback where progesterone receptor (PGR) suppresses the E2 activity through ER1 by inhibiting its expression. This facilitates the induction of PGR expression in the endometrium [88]. An increasing body of evidence shows altered expression of progesterone receptors (PR), particularly reduced levels of PR-B in endometrial implants. Progesterone resistance is thought to be caused by loss or decrease in expression of PR in endometriosis [89]. Consequently, aberrant expression of various genes associated with progesterone regulation, such as *Bcl2*, *FOXO1A* [90], and *HSD17B2*, has been reported in women with endometriosis [91]. miR-21-5p has been found to be linked with PGR expression. Another protein, YAP1, regulates the levels of miR-21-5p in endometrial tissue and both of them inversely correlate with the PGR levels. Findings further support that administration of dienogest by patients with endometriosis reports lower serum levels of miRNA21-5p [25,92]. Hence, it may serve as a good marker for endometriosis diagnosis.

3.8. Dysregulation of apoptotic pathways through miRNA expression

During menstruation, apoptosis aids in the regulated loss of endometrial tissue and is essential to preserving tissue homeostasis. However, in endometriosis this programmed cell death may become dysregulated, resulting in aberrant endometrial cell survival and accumulation outside of the uterus [93]. Accumulated evidence suggests that

in women with endometriosis, the apoptotic index was significantly less compared to controls. This variation was mainly due to a substantial decline in apoptosis, suggesting that a higher number of surviving cells reach the peritoneal cavity [94]. Endometriosis can develop and progress as a result of dysregulation of apoptosis, which can support the survival, growth, and persistence of ectopic endometrial tissue. Apoptosis regulates angiogenesis, inflammation, fibrosis, and tissue turnover, all of which are important aspects of the pathophysiology of endometriosis [95]. Aberrant expression of *cir-miR-let-7*, *miR-200*, and *miR-125b* have been reported in women at different stages of endometriosis [96]. Findings suggest that these miRNAs are responsible for cancer progression, among which *miR-125b*, more specifically, is known to regulate apoptosis and proliferation. *miR-125b* interacts directly with *BMPRI1B*, a tumor suppressor implicated in ovarian cancer [97]. Findings further support that this binding site contains single-nucleotide polymorphisms that are linked with endometriosis susceptibility [98]. *miR-200a* and *miR-141* isolated from the plasma samples of women with stage I-II endometriosis show decreased expression. Among the *miR-200* family members that are significant in endometriosis, *miR-141* has been documented to promote the death of ectopic endometrial cells by targeting *KLF-12* (Protein-Kruppel-like factor 12). Hence, lower levels of *miR-141* effectively regulate apoptosis [99]. According to the study, women with endometriosis had higher levels of *miR-30c-5p* expression in their serum. There are molecular similarities between endometriosis and cancer because the key cells in both conditions have the ability to avoid apoptosis. However, some research links endometriosis to a higher chance of developing endometrial and ovarian cancer [100]. Serum *miR-451a* (AUC = 0.8) levels in people were found to be positively linked with the *miR-451a* content of endometriotic lesions, and these individuals had considerably greater levels of serum *miR-451a* than the control group [101,102]. The impaired cell survival due to overexpression of *miR-451a* has been speculated to control excessive cell proliferation in ectopic lesions. In primate model of endometriosis, it has been validated that *miR-451* plays an essential role in apoptosis. It has been reported that *miR-451* binds to a gene *YWHAZ* that encodes a protein 14.3.3 which inhibits apoptosis and leads to cell proliferation [103]. Among numerous miRNAs isolated from the serum sample of endometriotic patients, *miR-125-5p* has been reported as the single most promising diagnostic biomarker for endometriosis. Additionally, other miRNAs, such as *miR-3613-5p* and *miR-451a*, enhance the diagnostic efficacy when used in conjunction [104].

3.9. Potential miRNA associated with ovarian dysfunction and infertility

According to research, between 30 and 50 % of women with endometriosis are infertile [105]. Endometriosis is characterised by functional and structural alterations in the ectopic endometrium and inner myometrium, which have an adverse effect on female fertility. Certain molecular processes related to implantation and embryonic development are also connected to altered endometrial receptivity in patients with endometriosis [106]. Understanding the complex relationship between endometriosis and infertility requires disentangling several distinct paths. There are several contributing factors to infertility in endometriosis-affected women. Although it is still unclear how endometriosis affects ovarian functions, ovarian dysfunction may be one of the causes of infertility linked to the disease. In women with endometriosis, abnormal follicular growth from the early to the periovulatory stage may lead to a high frequency of low-quality oocytes and a decreased ovarian reserve. The steroid production pathway may be linked to ovarian dysfunction [107]. One of the most studied biochemical aspects associated with endometrial-induced infertility is oxidative stress. Thus, oxidative stress events linked to modifications in the peritoneal, serum, and/or follicular microenvironments may lead to low-quality oocytes and jeopardise the ability of women to reproduce [108]. Elevated serum levels of indicators including nitrates/nitrites and advanced oxidation protein products has been reported in patients with

advanced stages of endometriosis. Biochemical imbalances have been reported in such women following surgery for gynecological disorders [109,110]. Consequently, there is research that shows a differential pattern of expression for *miR-150-5p*, *miR-150-3p*, *miR-149-5p*, and *miR-146b-3p* in the endometrium as well as consistent direction changes in blood samples for *miR-342-3p* in patients suffering from recurrent implantation failure. Pathway enrichment analysis showed the involvement of these miRNAs in pathways associated with embryo implantation [111]. Research indicates that the disproportion in the *miR22-5p* expression may be involved in stage I/II endometriosis-associated infertility. Although the exact mechanism of *miR22-5p* in infertility is not known, it may be involved in the regulation of ER2 expression [112]. With multiple roles in endometriosis-related mechanisms, *miR-199a*, *miR-122*, and *miR-542-3p* have been reported to be linked to the endometriosis fertility index and may be utilized to predict fertility prior to surgery. Additionally, it has shown as sensitivity and specificity of 79.6 and 73.5 % respectively when combined with CA125 marker and *miR-145* for minimal/mild endometriosis compared to stage III/IV [44]. However further research is needed in confirming its significance in determining female fertility [44]. Table 1 summarizes the Dysregulated expression of various miRNAs isolated from bodily fluid involved in endometriosis-associated mechanisms.

4. Putative role of exosomal miRNAs in endometriosis

MiRNAs are transferred to recipient cells in the form of exosomes, where they alter their function. Exosomal miRNA has been implicated in numerous important endometriosis pathophysiological processes, including angiogenesis, ectopic lesion growth, migration, and immune stimulation. Exosomal miRNAs isolated from endometriotic lesions, peritoneal fluid, and serum/plasma have been shown to express differently in endometriosis-affected women when compared to control subjects [116,117]. There is a research focus on the increased expression of serum exosomal *miR-22-3p*, which in turn enhances the proliferation, migration, and invasion of ectopic endometrial stem cells. *miR-22-3p* may function as a novel target for the regulation of EMS development by modulating the SIRT1/NF- κ B pathway. *miR-22-3p* also shows a positive correlation with the stages of endometriosis. Increased levels of exosomal serum *miR-320a* have been reported in patients with endometriosis compared to healthy individuals. *miR-320a* regulates non-small-cell lung cancer metastasis and invasion via the PI3K/Akt pathway. Evidence supports the suppression of cell proliferation and metastasis in lung adenocarcinoma by targeting the STAT3 signal. PI3K/Akt and STAT3 pathways are known to be involved in the pathogenesis of endometriosis [118]. Some of the exosomal miRNAs with significant roles in the pathogenesis of endometriosis have been discussed in Table 2.

5. Other miRNAs exhibiting different mechanisms studied in ectopic tissue in endometriosis

Since miRNAs have intricate regulatory networks, it is possible that a variety of pathways contribute to the pathophysiology of endometriosis as a result of their dysregulation in ectopic endometrial tissue. Although, compared to the endometrium, endometriotic lesions have greater cellular heterogeneity. Tissue heterogeneity may obscure miRNAs unique to endometriosis. Furthermore, for diagnosing endometriosis examination of microRNAs from the endometrium involves an invasive approach. Reduced levels of *miR-23a* and *-23b* result in hormonal imbalance by suppressing the levels of gene *NR5A1*, which results in increased synthesis of estrogen [124]. *miR-135a*, *135b* and *miR-19-3p* reduce the gene expression of progesterone signaling molecule thereby facilitating progesterone resistance. In endometrial implants, upregulation in the production of certain cytokines such as TNF- α , TNF- β , and IL-1b leads to upregulation of *miR-320a* [125]. *miR-16* and *miR-199a* induce inflammation and proliferation in the implant and act as a

Table 1
Circulating miRNAs involved in endometriosis-associated mechanisms.

Endometriosis-associated mechanisms	Circulating-miRNAs involved	Bodily fluid	Expression Pattern in ES or ES-associated cancer type	Potential Target if known/Functional significance	References
Oxidative stress	miR-302a	Serum	Upregulated	Increased levels further promote inflammation and cell proliferation in the ectopic implant.	[23]
	miR-20a			Production of proinflammatory cytokines through NF-κB activation.	[25]
Inflammation	miR-210-3p	Serum	Upregulated	Prevent endometriotic cells from OS.	[26]
	miR-125b-5p			Positively associated with enhanced production of proinflammatory cytokines.	[25]
	Let-7b-5p			Expression pattern linked with increase in TNF-α, IL-1β, and other cytokines of inflammation	[29]
	miR-146b	Peritoneal fluid	Upregulated	Associated with pain and negatively regulates inflammation.	[30]
	miR-20a	Plasma	Downregulated	Inflammation by decreasing IRF5 levels.	[33]
	miR-17-5p			miR-20a in ovarian tissue specifically promotes neovascularization.	
				All three miRs supports local inflammation in moderate to severe endometriosis.	
		miR-22		Facilitates post-transcriptional inhibition of their up-regulated mRNA targets (BCL2, CDKN1α/p21)	
			Knockdown of miR-22 enhance NF-κB pathways.		
			Involved in the malignant transformation of endometriosis.		
	miR-17-5p/2a	Plasma	Downregulated	Targets TGF-β and IL-8	[34,35]
	miR-155	Serum	Upregulated	Downregulates immune response modulator <i>SHIP1</i> .	
EMT, cell migration, invasion, adhesion, metastasis, cancer progression and development				Contributes to compromised B, T, and dendritic cell growth and function.	
	miR-29a-3p	Serum	Downregulated in DIE	Controls the expression of IL-12 in dendritic cells.	[39]
				Targets the VEGFA/CDC42/PAK1 signaling pathway.	
	miR-28-5p				Attenuates the proliferation and migration of tumor cells.
	miR-29a-5p		Differential	Tumor suppressor, stimulates cell proliferation leading to tumor development by reducing the expression of <i>MTSS1</i> .	[41,42]
				Discriminates between endometriotic patients with stage I and stage II and those without endometriosis.	
	miR-199a	Serum	Upregulated	Strongly linked with the location of adhesion and dissemination of lesions and proliferation.	[43]
	miR-145-5p	Plasma	Upregulation	Regulates cell proliferation and migration.	[45]
				Modulates signaling pathways such as SOX2, KLF5, TAGLN2.	
	miR-125b-5p	Serum		Sensitivity: 100 %; Specificity: 96 %.	[104,113]
	miR-196b-5p	Plasma	Downregulated	Invasion, pathogenesis of cancer.	
				Some of the top predicted target genes includes <i>HOXC8</i> , <i>HOXA7</i> , and <i>HOXB8</i> .	[47]
				Known to activate NF-κB signaling by directly targeting NFκBIA in lung cancer.	
		miR-378a-3p		Some target gene includes <i>KLK4</i> , <i>WDR31</i> .	
		miR-154-5p		Potential marker in endometrial carcinomas and participates in EMT.	
			High sensitivity and specificity (67 % and 68 %) at cut-off value of 5.2		
			Promising biomarker for cancer.	[50]	
	miR-326	Plasma/	Downregulated	Negatively regulates ectopic lesion implantation.	[51]
	miR-485-3p	Serum		Stop EMT by focusing on <i>MALAT1</i> in endometriosis and by suppressing the expression of <i>ZEB1</i> and <i>ZEB2</i> .	
	miR-196b	Plasma	Downregulated	A positive correlation with local invasion in breast cancer cells.	[56,73]
	miR-200 family	Plasma/		Target gene <i>ZNF652</i> in breast cancer.	
		Serum	Upregulated	Associated with endometrial cancer stage.	
	miR-155			Target genes <i>SPRY4</i> and <i>DAX1</i> .	[58]
	miR-181	Serum	Upregulated	Correlation between miR-135a and <i>HOX10</i> reported in endometriosis and ovarian cancer.	[46]
	miR-135a	Serum	Downregulated	Target sites include <i>HOXA10</i> , <i>VLDLR</i> , and <i>CSF1</i> .	
				Targeted genes positively regulate Wnt signaling pathways and apoptosis.	
	Let-7b	Serum	Downregulated	Target genes include <i>HOXA9</i> , <i>HMGA2</i> , and others involved in cancer.	
				Regulation of cell cycle control and p53 proteins	

(continued on next page)

Table 1 (continued)

Endometriosis-associated mechanisms	Circulating-miRNAs involved	Bodily fluid	Expression Pattern in ES or ES-associated cancer type	Potential Target if known/Functional significance	References
Angiogenesis	miR-486-5p	Serum Peritoneal fluid	Upregulated in EAO compared to control (ovarian endometrioma)	(involved in p53 signaling pathway). Inversely associated with cyclin D1 expression (regulate cell proliferation). Increase proliferation rate.	[75]
	miR-223 miR-204 miR-186 miR-222 (In combination)	Serum	–	Diagnostic biomarker of endometriosis associated cancers.	[76,77]
	miR-20a	Serum	–	Regulates <i>NTN4</i> expression, contributing to endometriosis. Targets <i>TSP-1</i> and promotes neovascularization. Known to Modulate endothelial function. Less explored.	[24,114, 115]
	miR-130a miR-27b miR-210 miR-199a		Upregulated		[79]
			Upregulated	Increase in hypoxic environments. Decreases the angiogenic capacity of endometrial stem cells by blocking the HIF-1 α /VEGF-A pathway. Regulation of vascularization under hypoxic condition.	[80]
Estrogen Signaling and Progesterone resistance	miR-33a-5p	Plasma	Upregulated	Regulation of vascularization under hypoxic condition.	[81]
	miR-145-5p Let-7 family (let-7b)	Serum Serum	Upregulated Upregulated	Modulates endothelial function.	[45]
	miR-21-5p	Plasma Serum	Upregulated	–	[85,86]
Apoptosis				Linked with PGR expression. Protein YAP1 regulates levels of miR-21-5p in endometrial tissue. Potential for detection of ovarian endometrioma. Higher E2 levels (high local E2 synthesis). Associated with elevated IL-8 and IL-6 serum levels	[90,91]
	miR-145 miR-141 miR-9	Serum	Downregulated specifically in Ovarian endometriosis.		[44]
	Let-7	Plasma	Downregulated	Low levels of let-7 family cause enhanced ER-A expression leading to decrease apoptosis. Regulates proliferation of cell and apoptosis. Regulate apoptosis and proliferation. miR-125b interacts directly with <i>BMPRI1B</i> . targets 3'UTRs of human p53 mRNAs; reduced p21; reduced apoptosis. Involved in ovarian cancer.	[96,97]
	miR-200 miR-125b				
	miR-141	Plasma	Downregulated in Stage I/II endometriosis	Targets Kruppel-like factor 12. Promote death of ectopic endometrial cells.	[99]
Ovarian dysfunction, Infertility,	miR-30c-5p miR451 (miR-451a) miR-3613-5p miR-451a (in combination)	Serum	Upregulated	Inhibits apoptosis. miR-451 target gene <i>YWHAZ</i> . Inhibition of apoptosis causing cell proliferation. Improved diagnostic performance.	[100]
			Downregulated		[103,104]
			Upregulated in ES compared to control (dermoid cyst, serous cystadenoma, simple ovarian cyst, others)		[104]
	miR-150-5p miR-150-3p miR-342-3p miR-146b-3p miR-149-5p miR-199a miR-122 miR-542-3p	Plasma	Upregulated	Biochemical imbalances. Recurrent implantation failure.	[111]
		Serum	Downregulated Upregulated with increase in endometriosis fertility index	Related to fertility index.	[44]

mediator of COX2 [23]. Ectopic endometrial tissue exhibits overexpression of the miR-17-92 cluster. This cluster is linked to the regulation of apoptosis, angiogenesis, cell proliferation, and tumor development [126]. Its overexpression in endometriosis may facilitate the emergence of new blood vessels within endometriotic lesions and the survival of cells [127]. Recent findings have suggested lower circulating levels of miR-103a-3p in endometriosis-affected women compared to control and it represents a unique endometriosis potential marker [128]. There are huge numbers of tissue-specific miRNAs contributing to endometriosis but requires invasive approach to study.

6. Challenges and limitations in miRNAQ

Endometriosis is a complex and heterogeneous condition that extends to molecular level. Different subtypes and stages may exhibit distinct miRNA expression patterns and identifying a specific miRNA that can reliably diagnose all subtypes is challenging. miRNAs can be isolated from various sources including whole blood, plasma, serum, peritoneal fluid, endometrial tissue, and ectopic lesions. The miRNA profiles may significantly differ between these sample type which may result in biological sample variability. Inadequate sample size for clinical studies complicates the comprehensive translational research. Standardization of sample collection and processing methods is crucial for the reproducibility and reliability of miRNA-based diagnostic assays.

Table 2
Aberrant expression of exosomal miRNAs in endometriosis.

Exosomal-miRNAs	Sample type	Expression pattern	Major findings	References
miR-215-5p, miR-26b-5p, miR-6795	Serum	Downregulated Upregulated	Related to the severity of the disease. Target genes (<i>PTEN</i>) are primarily involved in the MAPK and PI3k-AKT signaling pathways. Role in cell proliferation, angiogenesis, and development of many tumor types.	[119]
miR-130b, miR-4488, miR-432, miR-342, miR-425, miR-505, miR-6508, miR-365a, miR-365b, miR-451a, miR-486-5p, miR-130-5p	Peritoneal fluid	Differential expression in both early and advanced endometriosis compared to control Upregulated in patients with advanced endometriosis	Involved in immune modification and cell proliferation, cancer initiation and progression, and metastasis.	[120]
miR-145, miR-3b	Serum	Downregulated	Significantly decreased levels were obtained in samples isolated from both the proliferative and secretory phases of patients. Involved in regulating the implantation process. Potential role in cell differentiation, angiogenesis, and adhesion.	[121]
miR-361-5p, miR-19b-3p, let-7f-5p, miR-23a-3p, miR-199a-3p, miR-18a-5p, miR-221-3p, miR-17-5, miR-27a-3, and miR-25-3p	Plasma	Dysregulated	Linked with the proliferation in mesenchymal cells, the tumor necrosis factor (TNF) and Toll-like receptor signaling pathways. Involved in the differentiation of Th1 and Th2 cells.	[122]
miR-375, miR-27a-3p, and miR-30d-5p	Plasma	Downregulated	Implicated in endometrial pathologies such as chronic inflammation, cell proliferation, and migratory properties	[123]

However, variations in sample collection techniques, storage conditions, RNA extraction methods, and normalization strategies can introduce bias and confound the results. Small differences in sample handling protocols between studies can lead to inconsistencies and hinder the comparison of results across studies. Despite advances in miRNA research, the biological functions and regulatory mechanism of many miRNAs remain incompletely understood. This limits the interpretation of circulating miRNA profiles and their clinical utility in endometriosis diagnosis and management. Circ-miRNAs have the potential as a non-invasive endometriosis diagnostic tool. However, several issues need to be resolved before these biomarkers can be applied in therapeutic contexts. Working together, scientists, doctors, and industry partners can create standardized processes, verify findings, and further comprehend the intricate molecular processes underlying endometriosis.

7. Discussion and conclusion

Globally, the prevalence of endometriosis, an enigmatic gynaecological condition is rising. Inadequate diagnostic techniques exacerbate the issue by delaying treatment leading to worse outcomes. Endometriosis may develop as a result of multiple risk factors, including environmental factors, alcohol consumption, smoking, and obesity. However, research on the function of circulating miRNAs in the pathophysiology of endometriosis has gained momentum in recent years. The significance of these miRNAs in various disease-related biological processes has led to their identification as promising noninvasive biomarkers. MiRNAs linked to endometriosis have been found in serum/plasma or other body fluids, and this review may confirm the existence of endometriosis before it progresses to cancer. Numerous studies have reported dysregulated expression of circulating miRNAs in endometriosis patients compared to healthy controls. These dysregulated miRNAs are implicated in pathways related to inflammation, angiogenesis, cell proliferation, apoptosis, and hormonal signaling, all of which play critical roles in the pathogenesis of endometriosis. Among all, miR-199a and let-7 family are of utmost significance. Their involvement in various mechanisms associated with endometriosis makes them potential non-invasive biomarkers that need much more attention. Examining these non-invasive or less invasive biomarkers could give them an advantage over the current standard techniques for endometriosis diagnosis. However, the clinical utility of circulating miRNAs for endometriosis diagnosis remains to be fully validated in large-scale prospective studies. miRNAs exhibit fluctuations during different phases of menstrual cycle (proliferative and secretory) due to change in hormone levels. So, the cyclic variability may reduce their diagnostic accuracy and reproducibility. The miRNA expression profile can vary due to other confounding factors including age (age-related physiological changes) because of hormonal variation which may impact the result significantly. Moreover, some hormonal medications such as GnRH agonist, oral contraceptive pills significantly change the miRNAs involved in hormone-mediated pathways. The specificity of miRNAs found to be differently expressed in endometriosis may be diminished because they may also be linked to other gynecological disorders which can lead to misleading profiles. Additionally, studies on small populations and emphasizing findings that align with researchers hypothesis are some of the potential for biased interpretation. While existing evidence suggests dysregulated expression of circulating miRNAs in endometriosis patients and their involvement in disease pathophysiology, further research is needed to address several key challenges, including heterogeneity, specificity, and clinical validation. The roles of miRNAs in many metabolic pathways have not yet been fully understood. Additionally, this review would also showcase ongoing endeavors in the identification of miRNAs in many forms of cancer. Every day, researchers add specific miRNAs to databases and devote significant effort to comprehending the biogenesis of these small molecules. These scientific findings and methodologies are anticipated to enhance existing technology for therapy and biomarker identification. A better understanding of the function of circulating

miRNAs in endometriosis can potentially improve early detection, patient stratification, and personalized management of this debilitating condition. Collaborative efforts among researchers, clinicians, and industry partners are essential for translating these findings into clinically relevant applications and ultimately improving patient outcomes in endometriosis management.

8. Future perspective

Continued research efforts aimed at comprehensive miRNA profiling in endometriosis patients may lead to the discovery of novel miRNAs that are specifically dysregulated in the disease. Advanced high-throughput sequencing technologies combined with bioinformatics approaches can facilitate the identification of candidate miRNA biomarkers with high sensitivity and specificity. Multi-omics approaches may reveal complex regulatory networks and identify synergistic biomarker panels that improve diagnostic accuracy and predictive value. By integrating clinical data, imaging findings, and molecular biomarkers, machine learning models can develop robust algorithms for endometriosis diagnosis, patient stratification, and personalized treatment selection. Collaborative initiatives and consortia focused on method standardization and quality control can facilitate the translation of research findings into clinically applicable diagnostic assays. Advancements in microfluidic technology, biosensors, and point-of-care testing platforms enable the development of rapid and user-friendly assays for detecting circulating miRNA biomarkers at the point of care. Portable devices capable of sensitive and specific miRNA detection could facilitate decentralized testing, improve patient access to diagnostic services, and streamline clinical decision-making in resource-limited settings.

CRediT authorship contribution statement

Anuja Pant: Writing – original draft, Resources, Investigation, Conceptualization. **Kareena Moar:** Writing – review & editing, Data curation. **Taruna K. Arora:** Writing – review & editing, Resources. **Tikam Chand Dakal:** Writing – review & editing. **Vipin Ranga:** Writing – review & editing. **Narendra Kumar Sharma:** Writing – review & editing. **Pawan Kumar Maurya:** Writing – review & editing, Validation, Supervision, Resources, Funding acquisition, Formal analysis.

Consent to participate

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Declaration of competing interest

The authors declare that they have no known competing financial

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Abbreviations

BMPR1:	Bone Morphogenetic Protein Receptor Type 1A
CDC42:	Cell division control protein 42 homolog
COX2:	Cyclooxygenase2
CSF1:	Colony-stimulating Factor 1
DAX1:	Dosage-sensitive sex reversal
DAX1:	Dosage-sensitive sex-reversal, adrenal hypoplasia congenita critical region on the X-chromosome, gene 1
EAOC:	Endometriosis associated ovarian cancer
FOXO1A:	Forkhead box O1A
HMG2:	High Mobility Group AT-Hook 2
HOX:	Homeobox
HSD17B:	17 β -Hydroxysteroid dehydrogenases
IL:	Interleukin
KLF5:	Krüppel-like factor 5
KLK4:	Kallikrein
MALAT1:	Metastasis Associated Lung Adenocarcinoma Transcript 1
MTSS1:	Metastasis suppressor 1
NFkBIA:	Nuclear Factor kappa-B inhibitor, alpha
NR5A1:	Nuclear receptor subfamily 5 group A member 1
NTN4:	Netrin-4
PAK1:	p21-activated kinase 1 protein zeta
SHIP1:	SH-2 containing inositol 5' polyphosphatase 1
SOX2:	SRY (sex determining region Y)-box 2
SPRY4:	Sprouty RTK signaling antagonist 4
TAGLN2:	Transgelin-2
TGF:	Transforming Growth Factor
TNF:	Tumor Necrosis Factor
TSP-1:	Thrombospondin 1
VEGFA:	Vascular endothelial growth factor A
VLDLR:	Very Low-Density Lipoprotein Receptor
WDR31:	WD Repeat Domain 31
YAP1:	Yes-Associated Protein 1
YWHAZ:	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation
ZEB:	Zinc finger E-box Binding Homeobox 1
ZNF652:	Zinc Finger Protein 652

Data availability statement

No data was generated during the study of the literature review.

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