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REVIEW

MiRNAs related in signaling pathways of women's reproductive diseases: an overview

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Abstract

Background One of the main health issues that can affect women's health is reproductive diseases, such as polycystic ovary syndrome (PCOS), endometriosis (EMs), uterine leiomyomas (ULs), and ovarian cancer (OC). Although these diseases are very common, we do not have a complete understanding of their underlying cellular and molecular mechanisms. It is important to mention that the majority of patients are diagnosed with these diseases at later stages because of the absence of early diagnostic techniques and dependable molecular indicators. Hence, it is crucial to discover novel and non-invasive biomarkers that have prognostic, diagnostic and therapeutic capabilities. MiRNAs, also known as microRNAs, are small non-coding RNAs that play a crucial role in regulating gene expression at the post-transcriptional level. They are short in length, typically consisting of around 22 nucleotides, and are highly conserved across species. Numerous studies have shown that miRNAs are expressed differently in various diseases and can act as either oncogenes or tumor suppressors.

Methods The author conducted a comprehensive review of all the pertinent papers available in web of science, PubMed, Google Scholar, and Scopus databases.

Results We achieved three goals: providing readers with better information, enhancing search results, and making peer review easier.

Conclusions This review focuses on the investigation of miRNAs and their involvement in various reproductive disorders in women, including their molecular targets. Additionally, it explores the role of miRNAs in the development and progression of these disorders.

Keywords MiRNA · Biomarkers · Polycystic ovary syndrome (PCOS) · Endometriosis (EMs) · Uterine leiomyomas (ULs) · Ovarian cancer (OC)

Abbreviations

MiRNAs	MicroRNAs
PCOS	Polycystic ovarian syndrome
IR	Insulin resistance
KGN	Human granulosa tumor cells
CDKI	Cyclin-dependent kinase inhibitor
GC	Granulosa cell
PDCD4	Programmed cell death protein 4
TNF-α	Tumor necrosis factor α
ESR2	Estrogen receptor 2
CYP11A1	Cytochrome P450 family 11A1
OD	Oocyte donor
VDR	Vitamin D receptors
ET-1	Endothelin-1

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Foxa1	Forkhead box A1
GLUT4	Glucose transporter type 4
IRS1	Insulin receptor substrate 1
IGF-1	Insulin-like growth factor 1
EMs	Endometriosis
ESCs	Endometrial stromal cells
TLR-4	Toll-like receptor 4
LAMC2	Laminin-2
TFAP2C	Transcription factor AP-2
UPK1B	Uroplakin1B
FRAS1	Fraser syndrome 1
COL3A	Collagen type III A
ECSCs	Endometriotic cyst stromal cells
SMARCD1	Chromatin subfamily D member 1
MMP1	Matrix metallopeptidase 1
MMP-2	Matrix metalloproteinase-2
MMP-9	Matrix metalloproteinase-9
SIRT1	Sirtuin 1
KLF-12	Kruppel-like factor 12
KLF4	Krüppel-like factor 4
ZEB1	Zinc finger E-box binding homeobox 1
ZEB2	Zinc finger E-box binding homeobox 2
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
HOXA9	Homeobox A9
HOXA10	Homeobox A10
NTN4	Netrin-4
FGFR1	Fibroblast growth factor receptor
RTK	Receptor tyrosine kinase
PGR	Progesterone receptor
KLF9	Krüppel-like factor 9
ULs	Uterine leiomyomas
AUB	Abnormal uterine bleeding
ECM	Extracellular matrix
HMGA2	High motility group A2
OncomiR	Oncogenic miRNA
PKB	Protease kinase B
PAI-1	Plasminogen activator inhibitor-1
TF3	Tissue factor 3
CTGF	Connective tissue growth factor
IL-8	Interleukin-8
E2F1	E2F transcription factor 1
CCND1	Cyclin D1
IGFBP5	Insulin-like growth factor binding proteins 5
EMT	Epithelial-mesenchymal transition
LPCs	Leiomyoma progenitor cells
OC	Ovarian cancer
PARP	Poly ADP-ribose polymerase
PLK1	Polo-like kinase-1
RAD51AP1	RAD51-associated protein 1 gene
EAOC	Endometriosis-associated ovarian cancer
SOC	Serous ovarian cancer
OCCC	Ovarian clear cell cancer
ATG7	Autophagy-related protein 7
IGT	Impaired glucose tolerance
AR	Antiandrogenic
HEECs	Human endometrial epithelial cells
FOXP3	Forkhead box P3

Introduction

MicroRNAs (miRNAs) are single-stranded non-coding RNAs with an average of 22 nucleotides [1]. These molecules encode about 1% of the human genome sequences [2] and miRNAs regulate the expression of about 30% of mRNA [3]. MiRNAs play a key role in regulating biological processes through the regulation of gene expression at the post-transcriptional level [4–7]. The expression profile of miRNAs is unique in each tissue, disease, and normal condition [8, 9]. Therefore, the dysregulation of miRNA expression can be critical to the pathogenesis of various diseases, including women's reproductive disorders [7, 10–12], which are the main concern of modern women's health and may have a negative effect on fertility [13, 14]. The most common women's reproductive diseases include polycystic ovary syndrome (PCOS) [15], endometriosis (EMs) [16, 17], uterine leiomyomas (ULs) [18], and ovarian cancer (OC) [12, 19]. Since these diseases do not exhibit obvious symptoms at the onset, they are typically diagnosed during the advanced stage [20]. The mechanistic diagram of ovarian/uterine dysfunctions was shown in Fig. 1. In contrast, traditional diagnostic techniques like laparoscopy, ultrasonography, and protein biomarkers are both costly and time-consuming. Therefore, it is essential to discover new biomarkers in order to diagnose and treatment these diseases. Cellular miRNAs can be found in the cellular environment, while extracellular miRNAs (also known as circulating miRNAs) can be easily obtained from various body fluids such as serum, plasma, tears, saliva, urine, breast milk, colostrum, peritoneal fluid, cerebrospinal fluid, bronchial lavage, seminal fluid, and follicular fluid [21]. Additionally, circulating hormones or cytokines are less stable in blood compared to these molecules, making them excellent biomarkers for non-invasive diagnosis of female reproductive diseases. However, the main feature in using miRNAs as diagnostic biomarkers include identifying specific miRNAs applicable to a diverse range of patients and creating cost-effective and straightforward methods for analysing these molecules [11].

Consequently, this study aims to shed light how dysregulation of miRNA affects reproductive diseases in women as well as the signaling pathways that are associated with these conditions.

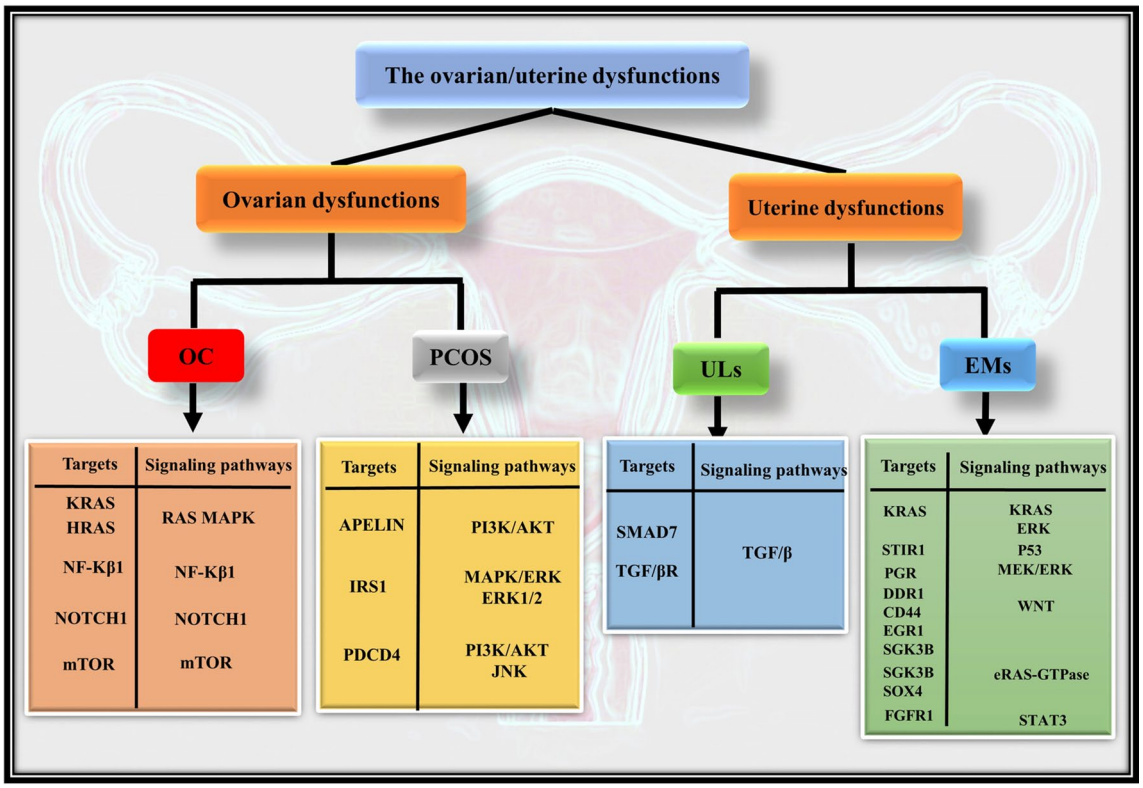

Fig. 1 A schematic of the targets and signaling pathways involved in ovarian and uterine dysfunctions

Polycystic ovary syndrome

Polycystic ovarian syndrome (PCOS) is a common reproductive endocrine syndrome in women of childbearing age, with an incidence of about 5–15% [22]. According to previous research, PCOS is usually accompanied by ovulatory dysfunction, hyperandrogenism, and insulin resistance (IR) [23]. Hence, PCOS is the cause of 40% of female infertility [24]. Some common symptoms of PCOS are a disrupted menstrual cycle, excessive hair growth, acne, being overweight, and infertility [25]. Currently, the etiology of PCOS is still unclear, but environmental and genetic factors, as well as alterations in the expression of miRNAs, may contribute to the pathogenesis of PCOS [15, 26]. Numerous studies have shown that abnormal levels of miRNAs can play a significant role in the pathogenesis and diagnosis of PCOS patients, often targeting key signaling pathways [27, 28]. Long et al. discovered that some miRNAs, namely miR-222, miR-16, miR-19a, miR-24, and miR-186, were upregulated while miR-320 was downregulated in individuals with PCOS. These miRNAs were identified as new biomarkers for diagnosing PCOS [27]. MiR-222, among these miRNAs, has been found to be associated with the development of PCOS, with its levels increasing. When this miRNA is overexpressed, it can lead to a decrease in the expression of p27 Kip1 in human granulosa tumor cells (KGN). P27 Kip1 is a member of the CDKI family and plays a role as a tumor-suppressor gene, promoting apoptosis and regulating the cell cycle. Both miR-222 and its target, p27 Kip1, have been proposed as potential biomarkers for PCOS patients [29, 30]. The miR-16 has been found as a downregulated miRNA in ovarian cortex tissues and serums of PCOS patients. The overexpression of this miRNA promotes ovarian granulosa cell (GC) proliferation and suppresses apoptosis by directly targeting programmed cell death protein 4 (PDCD4) [31]. However, another study conducted by Wang et al. found that overexpressing miR-16 could actually inhibit GC growth and increase cell death in PCOS patients by targeting Apelin13 and inhibiting the PI3K/Akt pathway [32]. In PCOS patients, the miR-19a has been found to target tumor necrosis factor α (TNF-α), leading to the apoptosis of KGN cells. Additionally, a study conducted by Song et al. revealed that miR-186 and miR-135a were elevated in GCs of PCOS patients and had a detrimental impact on the function of GCs by inhibiting the expression of estrogen receptor 2 (ESR2). Therefore, the levels of miR-186 and miR-135a in the GCs are associated with the levels of serum estradiol in individuals with PCOS [33]. A research study discovered that the expression of miR-24 was downregulated in the follicular fluid and serum of women who have PCOS. This particular miRNA

plays a crucial role in the process of steroid hormone biosynthesis [34]. MiR-24 targets cytochrome P450 family 11A1 (CYP11A1), which is a critical enzyme involved in the biosynthesis of steroid hormones [35, 36]. A decrease in miR-24 levels could result in an increase in CYP11A1 expression, ultimately leading to an enhanced synthesis of androgens. The study suggests that miR-24 could be utilized as a diagnostic biomarker for PCOS [36].

In a separate study by Kong et al., it was observed that miR-9 was highly expressed in the follicular fluid of PCOS patients, leading to ovarian dysfunction by targeting vitamin D receptors (VDR) [37]. Moreover, Rashad et al. revealed that the levels of miR-320 were reduced in individuals with PCOS and it targeted the endothelin-1 (ET-1) gene [38]. The ET-1 gene is a powerful biomolecule peptide that plays a role in cell division, tumor growth, and mitosis [39, 40]. Similarly, Yuan et al. found that the expression of this particular miRNA was significantly decreased in the ovarian tissue of PCOS patients with insulin resistance (IR) compared to healthy individuals. Interestingly, they also found that this miRNA could regulate IR in PCOS patients by inhibiting the ERK1/2 pathway through targeting insulin receptor substrate 1 (IRS-1) [41]. Additionally, Sang et al. found that there was a significant decrease in miR-132 levels in the follicular fluid of patients with PCOS compared to healthy individuals [42]. However, another study observed an upregulation of miR-132 in GCs of PCOS patients [43]. MiR-132 directly targets forkhead box A1 (Foxa1), resulting in the suppression of KGN cell viability [43]. Foxa1 is a transcription factor that determines genomic regions for binding the other transcription factors, including estrogen, progesterone, and androgen receptors [44, 45]. In PCOS patients, Chen et al. discovered an overexpression of miR-93 in adipocytes. They observed that miR-93 upregulation resulted in a reduction of glucose transporter type 4 (GLUT4) gene expression [46]. GLUT4 is a crucial protein that facilitates glucose transportation to adipocytes via insulin, and its expression is decreased in adipocytes of PCOS patients, which affects glucose homeostasis [47]. One study revealed that miR-145 decreases in human GCs in PCOS patients. This miRNA could suppress human GC cell proliferation by targeting IRS1, leading to blocked MAPK/ERK signaling pathways in PCOS patients. This study also reported that high insulin levels decreased the expression of miR-145 in PCOS [48]. Xia et al. found that miR-155 was highly expressed in the ovarian cortical tissue of individuals with PCOS and could promote proliferation, migration, and invasion in human KGN cells. However, they also observed that this miRNA could decrease PDCD4 levels and trigger the PI3K/AKT and JNK signaling pathways [49]. Other studies have also found that this miRNA is multifunctional and is used as a biomarker for diagnosing PCOS [50, 51]. PDCD4 is a translational repressor that binds to the eIF4A factor and inhibits its RNA helicase activity [52, 53]. This protein is highly expressed in women with PCOS [54]. Geng et al. reported the relationship between miR-99a and PCOS. They found that miR-99a could promote the apoptosis of human GCs by targeting the 3′-UTR of insulin-like growth factor 1 receptor (IGF-1R). IGF-1R is a member of the transmembrane tyrosine kinase receptor family, activated by insulin-like growth factor 1 (IGF-1) or IGF-2. They also reported that the expression of this miRNA decreased in PCOS patients, whereas the protein level of IGF-1R increased [55].

Endometriosis

Endometriosis (EMs) is a multifactorial estrogen-dependent gynecologic condition. This disease affects approximately 10% of all reproductive-aged women worldwide [56]. The clinical symptoms of EMs typically include dysmenorrhea, chronic pelvic pain, dyspareunia, and infertility [57]. Several studies have indicated that this disease is also related to people's genetics [58–60]. The risk of EMs is seven times higher in women with a family history compared to other women [61]. EMs, despite being highly prevalent, is often difficult to detect due to its variable symptoms and complications in pathogenesis, resulting in delays in diagnosis [62]. There are various methods available for detecting this disease, such as imaging techniques, protein biomarkers, and laparoscopy [56]. Currently, laparoscopic surgery is considered the most reliable method for diagnosing EMs [63], but it is expensive and invasive. As a result, scientists have been exploring alternative diagnostic tests for EMs [56]. Numerous research studies have demonstrated the involvement of multiple miRNAs in the development of EMs, making them a desirable option for non-invasive detection of these diseases [64–67]. Moreover, miRNA levels have been observed to alter in EMs according to researchers [68].

In their ground-breaking study, Wang et al. discovered that the levels of certain miRNAs in the bloodstream can serve as sensitive markers for detecting endometriosis. They specifically found that miR-199a is associated with the typical symptoms of this condition, indicating its importance in hormone-related pathways. Through experimental analysis, they identified several target genes of miR-199a, including discoidin domain receptor 1 (DDR1), CD44, early growth response 1 (EGR1), and serine/threonine-protein kinase (SGK3B) in the Wnt signaling pathway, as well as SGK3B in the Ras-GTPase pathway. Additionally, the researchers observed that the combination of miR-199a and miR-122, by targeting SRY-related HMG box 4 (SOX4), showed an increase in serum levels and could potentially be used to differentiate the severity of endometriosis [69]. Furthermore, it was observed that the levels of miR-202 were reduced in the endometrial stromal cells (ESCs) of patients with

EMs. Additionally, by targeting K-Ras in the Raf-1/MEK/ERK signaling pathway, the overexpression of miR-202 was shown to hinder the invasion and migration of primary ESCs from patients with EMs [70]. The plasma levels of let-7b-5p are significantly downregulated in EMs [71]. The toll-like receptor 4 (TLR-4) gene is targeted by this miRNA, potentially contributing to the inflammation involved in the pathophysiology of EMs [72]. Furthermore, the let-7 family has been shown to target the KRAS gene, which is part of the KRAS pathway that is targeted for therapeutic treatment of EMs [73]. Hawkins et al. discovered that certain miRNAs exhibited altered expression in EMs as compared to the endometrium. One of these miRNAs, miR-29c, targeted the 3′-UTR of several extracellular matrix genes, including laminin subunit gamma 2 (LAMC2), transcription factor AP-2 gamma (TFAP2C), uroplakin 1B (UPK1B), and fraser syndrome 1 (FRAS1). To confirm these targets, a luciferase reporter was used, revealing that miR-29c targets the 3′-UTRs of collagen type III alpha 1 chain (COL3A), collagen type VII alpha 1 chain (COL7A1), collagen type XXI alpha 1 Chain (COL21A1), and TFAP2C mRNAs [74]. A different research demonstrated that the levels of miR-29c were reduced in individuals with EMs. This specific miRNA has the ability to suppress the progression of EMs by impacting the invasion of the endometrium, the growth of cells, and programmed cell death, all by suppressing the expression of c-Jun. Consequently, targeting miR-29c could potentially be a novel approach for the treatment of EMs [75]. Takebayashi et al. discovered that there was an increase in the expression of miR-100-5p in stromal cells of human endometriotic cysts (ECSCs). They found that miR-100-5p directly targeted two genes, namely SWItch/sucrose non-fermentable-related matrix-associated actin-dependent regulator of chromatin subfamily D member 1 (SMARCD1) and matrix metallopeptidase 1 (MMP1) [76]. Furthermore, numerous research studies have discovered that the levels of miR-34a expression were significantly decreased in EM tissues. This decrease in miR-34a expression has been found to have an impact on the p53 protein by inhibiting sirtuin 1 (SIRT1) [77, 78]. It is worth noting that SIRT1plays a crucial role in regulating the homeostasis of vascular endothelial cells [79, 80]. Mounting evidence indicates that the miR-200 family, including miR-141-3p, miR-200a, miR-200b, and miR-200c, changes in the plasma levels of patients with EMs. This family can serve as potential non-invasive biomarkers for diagnosing EMs [81]. Kruppel-like factor 12 (KLF-12) is a transcription factor and plays a regulatory role in some cell processes such as cell differentiation, physiologic function, and phenotypic modulation [82]. It has been reported that miR-141-3p significantly decreases in ectopic ESCs. This miRNA targets KLF-12 mRNA, which leads to the suppression of cell proliferation and migration [83]. In a study by Rekker et al., it was found that the levels of miR-200a and miR-141 were lower in the plasma of women with EMs compared to those who were healthy. The study indicated that these two microRNAs could potentially serve as novel non-invasive biomarkers for diagnosing EMs [81]. while the search results suggest that miR-200a may play a role in endometriosis, the findings are not entirely consistent and further research is needed to fully understand its mechanisms of action in the disease. A different research showed that the levels of miR-200b were reduced in individuals with EMs and this had an impact on the growth and spread of endometriotic cells. This was achieved by targeting three proteins: krüppel-like factor 4 (KLF4), zinc finger E-box binding homeobox 1 (ZEB1), and zinc finger E-box binding homeobox 2 (ZEB2) [84]. Moreover, miR-200c is strikingly downregulated in ectopic endometrial compared with normal endometrial tissues. This miRNA represses EMs by targeting metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) [85]. In another study, Rekker et al. showed that the expression of miR-139-5p and miR-375 increased and decreased, respectively, in endometriotic lesions compared to eutopic cells. Overexpression of miR-139-5p resulted in the suppression of homeobox A9 (HOXA9) and homeobox A10 (HOXA10), while miR-375 was responsible for regulating the endothelin 1 (EDN1) gene [86]. Overall, the exact mechanisms by which miR-139-5p and miR-375 contribute to endometriosis development are not fully understood and require further investigation. However, the search results suggest that these miRNAs may be involved in multiple processes that are dysregulated in endometriosis, including cell proliferation, apoptosis, inflammation, metabolism, and angiogenesis [86]. Multiple pieces of evidence have indicated that miR-145 is a molecular marker that can be used non-invasively to diagnose EMs in patients at an early stage. This miRNA supresses the growth and invasion of endometriotic cells by targeting various factors related to pluripotency (SOX2) and cytoskeletal components (JAM-A and transgelin) [87, 88]. Several research studies have shown that the relationship between miR-126 and CRK proto-oncogene (Crk) can impact the growth and advancement of EMs. Crk has the ability to bind to various signaling molecules using its SH2/SH3 domain. This protein is essential for important cellular processes such as cell proliferation, migration, morphogenesis, invasion, phagocytosis, and survival, and is therefore involved in transmitting cellular signals. As a result, it plays a significant role in EMs [89, 90].

In a separate investigation, Jia et al. discovered that, miR-20a was notably decreased in EMs patients when compared to healthy individuals [91]. Interestingly, another study reported an increase in miR-20a in females with EMs in contrast to controls (women with benign ovarian tumors). However, the upregulation of this miRNA was only observed in stages III and IV (advanced stage) and not in stages I and II (mild stage). Additionally, miR-20a has an impact on

netrin-4 (NTN4) in EMs [92]. NTN4 is a secreted protein that plays a crucial role in various biological processes such as angiogenesis, tumorigenesis, cell migration, and invasion [93, 94]. Additionally, miR-424-5p is underexpressed in the ectopic endometrium and controls proliferation and apoptosis in EM cells via targeting fibroblast growth factor receptor (FGFR1) in the STAT3 signaling pathway [95]. FGFR1 is a growth factor receptor tyrosine kinase (RTK) involved in cellular processes such as cell proliferation and migration, angiogenesis, and the suppression of apoptosis [96]. In their study, Ma et al. reported that the levels of miR-142-3p decreased in ectopic endometrial tissues, while the expression of krüppel-like factor 9 (KLF9) increased, indicating that KLF9 is targeted by miR-142-3p [97]. KLF9 is known to have a significant impact on abnormal estrogen levels and acts as a progesterone receptor in endometriosis [98, 99]. Zhou et al. revealed that miR-196a was significantly upregulated in patients with EMs (mild stage). This miRNA decreases the expression of progesterone receptor (PGR) isoforms via the activation of the MEK/ERK signaling pathway and repress the progesterone receptor and decidualization in eutopic endometrium from women with EMs. This suggests that miR-196a may be involved in the resistance to progestin therapy that is often observed in EMs [100].

Uterine leiomyomas

Uterine leiomyomas (ULs), known as fibroids or myomas, are benign cancers of uterine smooth muscles (myometrium) and the most common pelvic tumors [18]. ULs mainly affect females during their childbearing years [101]. Most women with ULs are asymptomatic, but about 30% of them show different symptoms, including pelvic and back pain, abnormal uterine bleeding (AUB), anemia, constipation, urinary frequency, recurrent pregnancy loss, and infertility, which can eventually lead to a hysterectomy [102]. This disease was diagnosed in more than 70% of white women and more than 80% of African women [103, 104]. Despite the high prevalence of ULs, their cellular and molecular bases are not entirely understood. However, some alternations in genetics, epigenetics, the expression of miRNAs, steroids (estrogen and progesterone), the disorganized extracellular matrix (ECM), chemokines, cytokines, and growth factors play an important role in the formation and development of ULs [105].

Numerous pieces of evidence have shown that many miRNAs are expressed differently in leiomyoma compared to normal myometrium tissue [106–108]. Therefore, it can be argued that miRNAs regulate gene expression in this cancer [105]. The expression of let-7 family miRNAs is significantly upregulated in fibroids relative to the myometrium and is associated with fibroid size. Indeed, small fibroids ($\leq$3 cm) have a higher expression of let-7 family miRNAs compared to large fibroids ($\geq$10 cm) [106]. Klemke et al. and Peng et al. showed that let-7 family miRNAs suppressed the expression of high motility group A2 (HMGA2) genes in vitro and in vivo. Thus, they contribute to fibroid growth and development [109, 110]. The miR-21 has been reported as a highly upregulated miRNA in fibroids [106]. Furthermore, this miRNA is overexpressed as an oncogenic miRNA (oncomiR) in the (hTERT)-immortalized leiomyoma cell line (UtLM) and leiomyoma tissue. Therefore, it can cause apoptosis and translation by binding to the mRNA of molecules involved in these processes [111]. On the other hand, PDCD-4 is a potential target for miR-21. Unexpectedly, the overexpression of miR-21 increases the expression of PDCD-4 at the protein level in ULs, while the expression of this molecule decreases in most cancers and acts as a tumor suppressor [111]. Interestingly, miR-21, both directly and indirectly, affects the TGF/β pathway by suppressing SMAD7 and the TGF/β receptor, respectively, and increases ECM formation in fibroids [112]. Cardozo et al. showed that the overexpression of miR-21a-5p increased the expression of TGF/β3 protein in fibroids and altered the expression of several genes, including matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), fibronectin, and collagen. According to these findings, the overexpression of miR-21 can increase proliferation in UL cells [113]. The miR-29 family (miR-29a, miR-29b, and miR-29c), especially miR-29b and miR-29c, is significantly downregulated in leiomyoma relative to the myometrium [107]. This family generally targets more than 15 ECM-related genes, including collagen subtypes and elastin in fibroids [114]. The miRNAs from this family directly bind to the 3`-UTR of collagen type I and inhibit the translation of this protein [114]. Therefore, the downregulation of the miR-29 members increases the collagen fibers in leiomyoma [115, 116]. Xu et al. found that this family could directly or indirectly regulate the expression of several genes in the protease kinase B (PKB or AKT) pathway, increasing growth and survival in response to extracellular signals [117]. Another study revealed that miR-29c could target CDK (a key regulator of the G1/S phase). Thus, increasing the expression of miR-29c in fibroids inhibits the expression of CDK, and the knockdown of this miRNA increases the expression of CDK [118]. The two miR-93 and miR-106 families have overlapping functions in fibroids [119]. Melo et al. showed that miR-93 and miR-106b had lower expression levels in fibroids than in the myometrium and were predicted to be regulators of the HMGA2 gene [120]. Furthermore, miR-93 and miR-106b can directly or indirectly regulate the expression of several factors, including plasminogen activator inhibitor-1 (PAI-1), tissue factor 3 (TF3), connective tissue growth factor (CTGF), and interleukin-8 (IL-8), which are associated with inflammation and tissue turnover. Accordingly, these two miRNAs can play an

important role in fibroid biology [121]. Furthermore, it has been shown that miR-93 targets E2F transcription factor 1 (E2F1) and cyclin D1 (CCND1) in primary uterine fibroid cells [118]. The miR-197 is a miRNA tumor suppressor, the expression of which is reduced in human UFs. This miRNA induces apoptosis and inhibits cell proliferation and migration in vitro [122, 123]. Ling et al. found that the downregulation of miR-197 could increase cell growth and stop the cell cycle in the G0/G1 phase in human UL cells. It has also been shown that miR-197 inhibits cell proliferation by directly targeting insulin-like growth factor binding proteins 5 (IGFBP5) [124]. Numerous pieces of evidence have shown that miR-200a, miR-200b, and miR-200c (especially miR-200c) are significantly downregulated in ULs compared to the healthy surrounding uterine tissue [119]. The miR-200 family may act as tumor suppressors by inhibiting epithelial-mesenchymal transition (EMT) [125]. Furthermore, these miRNAs regulate the activation of the NF-kB pathway via the phosphorylation of its inhibitor [121]. Like the miR-29 family, the miR-200 family regulates the expression of several genes in the AKT pathway [117]. Additionally, miR-200c, like miR-29c, targets CDK2 mRNA in fibroids [118].

Ovarian cancer

Ovarian cancer (OC) is one of the most common gynecologic malignancies, ranking third after cervical and uterine cancers [126, 127]. This cancer has a high mortality rate, and it is estimated that deaths from OC will increase significantly by 2040 [127]. The therapeutic options for OC have been remarkably improved by identifying invasive surgical methods and new drug treatments [128]. Recently, several clinical trials have shown that poly (ADP-ribose) polymerase (PARP) inhibitors (namely olaparib, niraparib, talazoparib, and rucaparib) are effective in patients with platinum-resistant or sensitive OC with BReast CAncer gene 1 (BRCA1) or BReast CAncer gene 1 (BRCA2) mutations [129, 130]. Hence, these inhibitors can be a turning point in treating OC in the early stages and in tumor recurrence [131]. Besides these novel therapeutic methods, multidisciplinary approaches with different specialists are needed to treat OC to determine the treatment protocol for each patient based on the patient's characteristics and the tumor state [132, 133]. On the other hand, the symptoms of OC are often absent or vague at the onset of the disease, and due to the lack of early diagnostic methods and reliable molecular markers, most patients are diagnosed at an advanced stage, and only 20% of them are diagnosed at stage I of the disease [20].

Recently, several studies have shown that changes in the expression profiling of miRNAs have been detected in OC. Hence, miRNAs can serve as new biomarkers with prognostic, diagnostic, and therapeutic approaches in this cancer [26, 154, 155]. Here, the most important miRNAs involved in the pathogenesis of OC and their molecular targets are discussed. The dysregulation of the miR-200 family and their role in the onset and progression of OC are well established [134]. Members of the miR-200 family suppress the expression of ZEB1 and ZEB2, which leads to the suppression of EMT [135]. Besides, this family affects the β-tubulin III protein in OC [136]. β-tubulin III is a microtubule protein normally expressed in cells of neuronal origin [137]. The overexpression of this protein has been reported in OC and is associated with poor survival and poor response to treatment [138]. The let-7 family is another family whose expression is significantly reduced in OC [139]. This family inhibits several oncogenes, such as KRAS, HRAS, c-MYC, and HMGA-2, and several cell cycle regulators, such as cyclin A, cyclin D1, cyclin D2, cyclin D3, CDC25, and CDK6, in OC [140–143]. Intriguingly, miR-34 family members (miR-34a, miR-34b, and miR-34c) are underexpressed in OC [144]. This family also targets several genes, including c-MYC, NOTCH1, CDK6, E2F3, MET, Bcl2, and cyclin D1 in OC [144, 145]. In addition, the expression of miR-100 decreases in most of the OC cell lines and tissues [5, 146]. This miRNA inhibits the mTOR signaling pathway and proto-oncogene of polo-like kinase-1 (PLK1) in OC [146, 147]. The miR-9 is a downregulated miRNA in human OC, and its overexpression inhibits OC cell growth [148]. This miRNA could directly bind to the 3′-UTR of NF-κB1 mRNA and suppress the NF-κB1 expression at both the mRNA and protein levels. Therefore, NF-κB1 is an important target of miR-9 in OC cells [148]. In addition, miR-140-3p is downregulated in OC and is a potential regulator of the RAD51-associated protein 1 gene (RAD51AP1) [149, 150]. The RAD51AP1 gene is involved in double-stranded DNA repair and is overexpressed in OC [149]. Furthermore, the dysregulation of miR-214 has been reported in OC. This miRNA induces cisplatin resistance and cell survival via targeting the 3'-UTR of PTEN mRNA, which leads to the suppression of PTEN protein and the activation of the PI3K/AKT/mTOR signaling pathway [151].

Infertility

Infertility is a global reproductive health problem that affects 10–15% of women worldwide, and women's reproductive disorders may have adverse effects on fertility [13, 14]. Implantation occurs as a result of complex communication between the blastocyst and endometrium. Some studies have demonstrated that the interaction between various genes and miRNAs could lead to the creation of signaling during implantation, thereby modulating the interaction between the embryo and endometrium [152]. Since miRNAs

are secreted from both the blastocyst and endometrium, we mention several examples of different expressions of miRNAs in implanted compared with non-implanted blastocysts and in the endometrium of women with recurrent implantation failure. Cuman et al. discovered that miR-661 is more highly expressed in blastocysts that do not successfully implant compared to those that do. It was found that when primary human endometrial epithelial cells (HEECs) take in miR-661, it reduces the attachment of trophoblast cell line spheroids to HEECs through poliovirus receptor-related 1 (PVRL1) [153]. This suggests that human blastocysts, through changes in miRNA secretion, can cause abnormalities that lead to failed implantation. In addition, certain research studies have indicated that miRNAs exhibit varying levels of expression during the menstrual cycle and that the irregularity of specific miRNAs can impact a woman's fertility [154–156]. One such example is the increase in endometrial miR-31 during the reproductive cycle, which targets the regulatory protein forkhead box P3 (FOXP3) that plays a role in immune system responses [157].

MiRNA-based therapeutics in PCOS, EMS, ULS, and OC

MiRNA-based therapeutics have shown promising results in the diagnosis and treatment of various reproductive women diseases. Recent research has shown that miRNAs and their target mRNAs are differentially expressed in EMs, OC, ULS and PCOS. Additionally, miRNAs have been found to regulate a wide range of normal and abnormal cellular functions, suggesting they may have significant roles in the development of these disorders. For example, a study revealed that the downregulation of miR-17-5P and the upregulation of autophagy-related protein 7 (ATG7) in PCOS patients could serve as therapeutic targets in these patients [158]. Moreover, several studies have demonstrated that the let-7 family targets the KRAS gene and that the KRAS pathway is one of the therapeutic targets for treating EMs [73]. Indeed, the local treatment of EMs with let-7b can be considered a promising treatment for EMs because this miRNA can simultaneously affect several signaling pathways, including estrogen, KRAS, and inflammatory signaling [72]. On the other hand, miR-21 is the most common miRNA that is differentially expressed in ULs and is regulated by estradiol. Recently, this miRNA has been a target for treating ULs [101]. The miR-199a-5p is another miRNA that could serve as an evolutionarily conserved anti-oncogene and a therapeutic target for ULs [159]. According to the study by Ahn et al., the expression level of miR-139-5p decreases in myeloma cells, and the modulation of miR-139-5p could be effective in the pathogenesis of ULs by regulating collagen type 1 and the phosphorylation of the p38 MAPK pathway. Therefore, this miRNA can be used as a new therapeutic target in ULs [160]. In patients with OC, reducing miR-150 and miR-214 expression can prevent the proliferation of cancer cells and the tolerance of chemotherapy drugs. Hence, these two miRNAs may be used as an adjuvant treatment in OC [161]. Lan et al. revealed that the downregulation of miR-140-5P can lead to a decrease in the sensitivity of OC cells to the drug cisplatin [162]. The upregulation of this miRNA can inhibit the proliferation and migration of cancer cells and increase the sensitivity to cisplatin; hence, it may be considered a therapeutic target in OC [163]. In addition, the upregulation of miR-21 is correlated with cisplatin resistance in OC, and targeting miR-21 as a therapeutic target can decrease the tumorigenic characteristics in cisplatin-resistant cells [164].

On the other hand, miRNAs could be used as biomarkers to monitor therapeutic efficacy. Metformin is an insulin-sensitizing drug that has been used for decades in PCOS patients. This drug improves IR and impaired glucose tolerance (IGT) and reduces androgen levels in PCOS patients through the possible reduction of the miR-222 expression level [163]. Moreover, treatments based on antiandrogenic (AR blockers), including ethinyl estradiol and cyproterone-acetate, deal with the excess amount of androgens in PCOS patients and increase the levels of miR-27 b and miR-155 [51]. Additionally, it has been reported that miR-125b expression levels change in ovarian endometriomas after treatment with leuprolide acetate. Therefore, this miRNA can be used as a potential biomarker in monitoring response to treatment [165]. Kiba et al. found that five miRNAs, including miR-15b, miR-125b-1, miR-136, miR-142-3p, and miR-146a, were upregulated in ovarian endometrioma after leuprolide acetate treatment [165]. Furthermore, let-7a can be served as a biomarker in monitoring the response to chemotherapy in OC patients. Indeed, let-7a upregulation was associated with increased survival rates in OC patients receiving platinum alone, but with lower survival in patients receiving combination therapy [166].

In the future, personalized medicine could benefit from the use of miRNA-based therapies. Nevertheless, there are still obstacles to overcome, such as standardization and a better comprehension of how miRNAs can be applied in personalized medicine. Despite these challenges, scientists are investigating the potential of miRNA-based therapies as a hopeful new method for treating a variety of illnesses.

Conclusions

Infertility and the risk of fetal and maternal mortality are largely attributed to common reproductive diseases in women, including PCOS, EMs, ULs, and OC. Early detection is crucial for effective treatment, but current

diagnostic methods are often time-consuming and expensive. However, miRNAs have emerged as significant players in various processes that impact the functioning of the female reproductive system. On the other hand, an ideal biomarker should meet certain criteria, such as enabling early detection, being easily accessible through non-invasive methods, being specific to each condition or tissue, exhibiting sensitivity, having a long half-life in samples, and allowing for accurate and reasonably priced detection. According to this review, miRNA signatures are different in healthy women compared to women with reproductive disorders (Fig. 2). MiRNAs play a significant role in regulating gene expression by targeting specific molecules, some of which are involved in signaling pathways. These pathways are crucial in the development of reproductive diseases in women, such as MAPK/ERK, PI3K/AKT, ERK1/2, KRAS, WNT, e Ras-GTPase, Adherens junction, Hippo, ECM-receptor interaction, TGF/β, P38 MAPK, NF-κB, NOTCH1, P53, STAT3, JNK, and mTOR.

In conclusion, using miRNAs presents a fresh method for identifying reproductive diseases. Consequently, miRNAs have been identified as particular diagnostic biomarkers implicated in the development of reproductive diseases. Our final goal in this study was to assess the impact of miRNAs and their targets on the pathogenesis and diagnosis of reproductive diseases in women (Table 1). Nonetheless, research on miRNAs in women's reproductive diseases is still in its early stages. However, there is a growing body of evidence that suggests that miRNAs have the potential to be used as biomarkers for diagnosis and as therapeutic targets. Moreover, there are several challenges in investigating the role of miRNAs in reproductive women diseases. These challenges include a limited understanding of miRNA function, difficulty in identifying the targets of miRNAs, variability in miRNA expression, lack of standardization in sample collection, RNA isolation, and data analysis, as well as high costs. However, despite these challenges, researchers are actively exploring

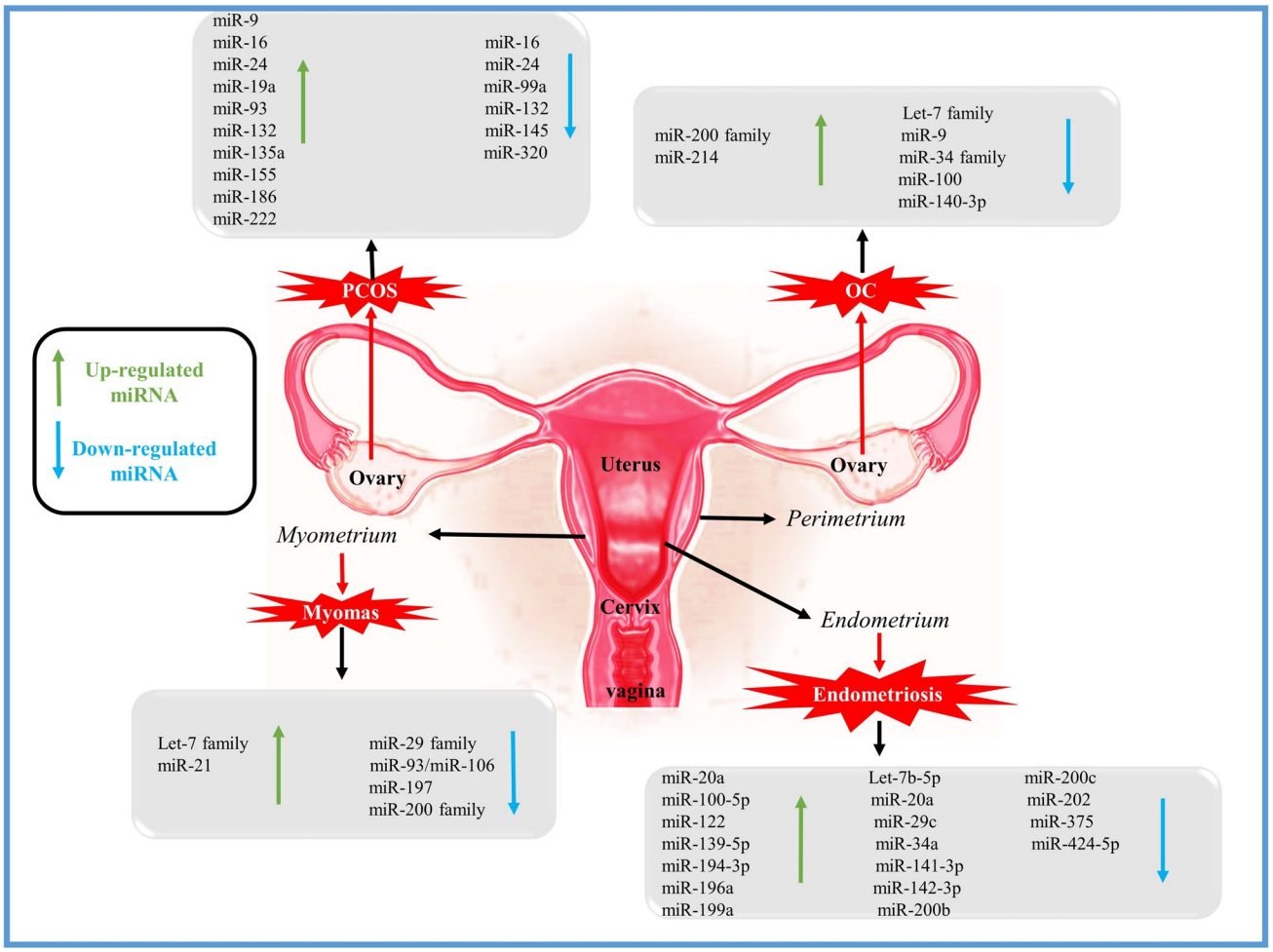

Fig. 2 A schematic of the female reproductive system and changes in miRNAs expression in PCOS polycystic ovarian syndrome, OC ovarian cancer, myomas/ULs/ fibroids, and endometriosis (EMs)

Table 1 MiRNAs involved in PCOS, EMs, Uls and OC

Disease	miRNA	Effect	Alternation	Target	Signaling pathway	Technique	References
PCOS	MiR-9	Dysfunction of ovarian	Upregulation	VDR	–	RT-qPCR	[37]
	MiR-16	–	Downregulation or upregulation	PDCD4 Apelin13	PI3K/AKT	QRT-PCR Luciferase assay Western blot	[31, 32]
	MiR-19a	Apoptosis of KGN cells	Upregulation	TNF-α	–	Dual-luciferase assay QPCR Western blot	[167]
	MiR-24	–	Downregulation or upregulation	CYP11A1	–	RT-qPCR	[27, 36]
	MiR-93	–	Upregulation	GLUT4	–	Real-time PCR Western blot MiRNA microarray Luciferase assay	[46]
	MiR-99a	Apoptosis of human GC	Downregulation	IGF-1R	–	QRT-PCR Western blot	[55]
	MiR-132	–	Downregulation or upregulation	Foxa1	–	RT-qPCR Luciferase assay Western blot	[42, 43]
	MiR-135a	–	Upregulation	ESR2	–	QRT-PCR Dual-luciferase assay Immunoblotting	[33]
	MiR-145	Suppression of human GC cell proliferation	Downregulation	IRS1	MAPK/ERK	Dual-luciferase assay Western blot QRT-PCR	[48]
	MiR-155	Proliferation, migration and invasion of human KGN cells	Upregulation	PDCD4	PI3K/AKT JNK	Luciferase assay QRT-PCR Western blot	[49]
	MiR-186	–	Upregulation	ESR2	–	QRT-PCR Dual-luciferase assay Immunoblotting	[33]
	MiR-222	–	Upregulation	p27 Kip1	–	QRT-PCR Dual-luciferase assay Western blot	[29]
	MiR-320	–	Downregulation	ET-1 IRS-1	– ERK1/2	Microarray Real-time PCR ELISA	[38, 41, 168]
EMs	Let-7b-5p	–	Downregulation	TLR-4 KRAS	– KRAS	QRT-PCR Immunohistochemistry Western blot Luciferase assay	[72, 73]
	MiR-20a	–	Downregulation or upregulation	NTN4	–	Microarray QPCR	[91, 92]
	MiR-29c	–	Downregulation	LAMC2 TFAP2C UPK1B FRAS1 COL3A COL7A1 COL21A1 c-Jun	–	Next-generation sequencing Luciferase assay RT-qPCR Western blot	[74, 75]

Table 1 (continued)

Disease	miRNA	Effect	Alternation	Target	Signaling pathway	Technique	References
	MiR-34a	–	Downregulation	SIRT1	P53	Northern blot Western blot Luciferase assay RT-PCR	[77, 78]
	MiR-100-5p	–	Upregulation	SMARCD1 MMP1	–	RT-PCR Microarray ELISA	[76]
	MiR-122	–	Upregulation	SOX4	–	QRT-PCR	[69]
	MiR-139-5p	–	Upregulation	HOXA9 HOXA10	–	Sequencing QRT-PCR	[86]
	MiR-141-3p	Supersession of cell proliferation and migration	Downregulation	KLF-12	–	Real-time PCR Western blot	[83]
	MiR-142-3p	–	Downregulation	KLF9	–	QRT-PCR Western blot Dual-luciferase assay FISH	[97]
	MiR-145	Inhabitation proliferation and invasion in endometriotic cell	–	SOX2 JAM-A Transgelin	–	QPCR Western blot	[87, 88]
	MiR-194-3p	–	Upregulation	PGR	–	QRT-PCR Western blot Luciferase assay	[169]
	MiR-196a	–	Upregulation	PGR	MEK/ERK	Microarray QRT-PCR Luciferase assay	[100]
	MiR-199a	–	Upregulation	DDR1 CD44 EGR1 SGK3B SGK3B SOX4	WNT e Ras-GTPase	QRT-PCR	[69]
	MiR-200b	–	Downregulation	KLF4 ZEB1 ZEB2	–	QPCR	[84]
	MiR-200c	–	Downregulation	MALAT1	–	Microarray QRT-PCR Dual-luciferase assay	[85]
	MiR-202	–	Downregulation	K-Ras	ERK	Microarray RT-qPCR Luciferase assay Western blot	[70]
	MiR-375	–	Downregulation	EDN1	–	Sequencing QRT-PCR	[86]
	MiR-424-5p	–	Downregulation	FGFR1	STAT3	QRT-PCR Luciferase assay Western blot	[95]
ULs	Let-7 family	Fibroid growth and development	Upregulation	HMGA2	–	Microarray QRT-PCR Northern blot In situ Hybridization Western blot Luciferase assay	[106, 109, 110]

Table 1 (continued)

Disease	miRNA	Effect	Alternation	Target	Signaling pathway	Technique	References
	MiR-21	OncomiR	Upregulation	PDCD-4 SMAD7 TGF/βR	– TGF/β TGF/β	Microarray QRT-PCR Northern blot Western blot	[106, 111, 112]
	MiR-29 family	Growth and survival	Downregulation	Collagen I Elastin CDK	–	Microarray Luciferase assay	[107, 114, 118]
	MiR-93/miR-106	Fibroid biology	Downregulation	HMGA2 PAI-1 TF3 CTGF IL-8 E2F1 CCND1	–	Luciferase assay Microarray	[118, 120]
	MiR-197	Tumor suppressor	Downregulation	IGFBP5	–	QRT-PCR In situ Hybridization Western blot Luciferase assay	[122–124]
	MiR-200 family	Tumor suppressor	Downregulation	EMT CDK2	–	Luciferase assay QRT-PCR Western blot	[117, 118]
OC	Let-7 family	–	Downregulation	KRAS HRAS c-MYC HMGA-2 Cyclin A Cyclin D1 Cyclin D2 Cyclin D3 CDC25 CDK6	RAS MAPK RAS MAPK – – – – – – – –	Microarray QRT-PCR	[139–141]
	MiR-9	–	Downregulation	NF-κB1	NF-κB	Real-time PCR Western blot	[148]
	MiR-34 family	–	Downregulation	c-MYC NOTCH1 CDK6 E2F3 MET Bcl2 Cyclin D1	– NOTCH1 – – – – –	QRT-PCR In situ hybridization	[144, 145]
	MiR-100	–	Downregulation	PLK1 mTOR	– mTOR	QPCR Luciferase assay Western blot	[5, 146]
	MiR-140-3p	–	Downregulation	RAD51AP1	–	Microarray	[149]
	MiR-200 family	Suppression of EMT	Upregulation	ZEB1/2 β-tubulin III	–	QRT-PCR Luciferase assay Microarray	[135, 136]
	MiR-214	Cisplatin resistance and cell survival	Upregulation	PTEN	PI3K/AKT/mTOR	Microarray QRT-PCR	[151]

the potential of miRNA-based therapies as a promising approach for treating various reproductive women diseases. As research progresses, new insights are expected to emerge that will help overcome these challenges and enhance our understanding of how miRNAs can be utilized in personalized medicine.

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