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MicroRNAs in Gynecological Cancers: Small molecules with big implications

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Abstract

Gynecological cancers (GCs) are often diagnosed at advanced stages, limiting the efficacy of available therapeutic options. Thus, there remains an urgent and unmet need for innovative research for the efficient clinical management of GC patients. Research over past several years has revealed the enormous promise of miRNAs. These small non-coding RNAs can aid in the diagnosis, prognosis and therapy of all major GCs, viz., ovarian cancers, cervical cancers and endometrial cancers. Mechanistic details of the miRNAs-mediated regulation of multiple biological functions are under constant investigation, and a number of miRNAs are now believed to influence growth, proliferation, invasion, metastasis, chemoresistance and the relapse of different GCs. Modulation of tumor microenvironment by miRNAs can possibly explain some of their reported biological effects. miRNA signatures have been proposed as biomarkers for the early detection of GCs, even the various subtypes of individual GCs. miRNA signatures are also being pursued as predictors of response to therapies. This review catalogs the knowledge gained from collective studies, so as to assess the progress made so far. It is time to ponder over the knowledge gained, so that more meaningful pre-clinical and translational studies can be designed to better realize the potential that miRNAs have to offer.

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Keywords

MicroRNAs; gynecological cancers; ovarian cancer; endometrial cancer; cervical cancer; proliferation; metastasis; drug resistance; tumor microenvironment; diagnosis and prognosis

1 Introduction

Gynecological cancers (GCs) are the cancers that originate from, and affect, women's reproductive organs such as cervix, ovary, uterus/endometrium, vagina and vulva. GCs originate in different places within a woman's pelvis, the area between the hip bones and below the stomach. Each GC is unique, with its own signs and symptoms, as well as risk factors. The risk for GCs increases with age. In the United States (US), almost 90,000 women are diagnosed with GCs every year, and more than 28,000 women die from these malignancies [1].Among the different GCs, ovarian, cervical and endometrial cancers are the most frequent and, thus, considered major women health issues. Although endometrial cancer (EC) is the most common GC among women, ovarian cancer (OC) is the most lethal type [2], and despite scientific advancements, mortality rates of GCs continue to rise [1]. Both early diagnosis and limited treatment options for advanced GCs are contributing factors to their high mortality, emphasizing the need for further advancements in these areas.

Recent years have witnessed growing interest in the field of microRNAs (also referred to as miRNAs/miRs) because of their potential to regulate diverse biological processes [3]. MicroRNAs are small, non-coding RNA molecules, approximately 20–22 nucleotides in length. In general, miRNAs regulate the expression of genes by binding to the 3′-untranslated regions (3′-UTRs) of target messenger-RNAs (mRNAs) with partial or full complementarity, resulting in either translational repression or degradation of target mRNAs [3]. Human genome encodes several thousand miRNAs and the knowledge about their identity and functions is constantly emerging. It is believed that miRNAs regulate the expression of more than one-third of all human genes [4]. In this review article, we discuss deregulation of miRNAs in GCs, their established or putative functions, and clinical and translational relevance. Considering the high incidence and mortality, we will mainly focus on ovarian, cervical and endometrial cancers as the representative GCs.

2 Dysregulation of miRNAs in gynecologic cancers

Dysregulation of miRNAs in GCs has been reported in multiple studies suggesting their pathobiological importance (Table 1). Here, we discuss some of these reports on the differential expression of miRNAs in ovarian, cervical and endometrial cancers.

2.1 Ovarian cancer

OC is the deadliest GC in the US [5] (Table 2). Approximately seventy percent of the patients with OC are diagnosed with advanced disease [6], resulting in poor prognosis, even with aggressive and immediate treatments. Several studies have reported miRNA profiling from serum, plasma and tissues of OC patients, and have successfully identified distinct miRNA signatures. Zhang *et al.* were the first to demonstrate differential expression of

miRNAs in OC [7]. Their study identified a copy number loss of the regions that harbor mir-15a and mir-16-1 in 23.9% of OC cases. Using deep sequencing of samples from normal and malignant ovarian tissues, Wyman *et al.* discovered six novel differentially-expressed miRNAs (miR-2114*, miR-2115*, miR-2116*, miR-2114*, miR-449* and miR-548q) [8]. In addition, their study also identified miRNAs that were differentially expressed in OC histologic subtypes. miR-449a was specific to serous, miR-499-5p/miR-375/miR196a/miR-196b/miR-182 were specific to endometrioid, and miR-486-5p/miR-144/miR-30a/miR-199a-5p were specific to clear cell carcinoma [8]. Based on miRNA microarray data obtained from analysis on normal ovarian surface epithelium and ovarian tumors, Shahab and coworkers identified forty-two miRNAs, out of which thirty-three were over-expressed and nine miRNAs were down-regulated in OC [9]. In a recent study, small RNA sequencing was performed on normal tubal and high-grade serous ovarian cancer samples leading to identification of differential expression of several miRNAs, of which 59 were known and 20 were novel [10]. Another recent study identified 1156 deregulated miRNAs in OC [11]. miR-1, miR-133a, and miR-451 were under-expressed while miR-141, miR-200a, miR-200c, and miR-3613 were significantly elevated in most of the OC patients. Resnick *et al.* investigated differentially expressed miRNAs in the serum of OC patients, and observed that miR-21, miR-29a, miR-92, miR-93 and miR-126 were significantly over-expressed, while miR-155, miR-127 and miR-99b were under-expressed [12]. From the plasma of patients with OC, a specific miRNA signature was detected. This included nineteen down-regulated and three over-expressed miRNAs in OC patients, as compared to plasma of controls [10]. Moreover, six miRNAs, miR-126, miR-150, miR-17, miR-20a, miR-106b, and miR-92a, were efficient enough to distinguish benign plasma from that of sample of OC patients. Nam *et al.*, using miRNA microarray, identified several de-regulated miRNAs [13]. In 17 out of 20 cases, miR-21 was most frequently up-regulated; while miR-125b was down-regulated in 19 of 20 patients [13]. Their study further identified distinct miRNA signatures in OC cases, as compared with normal ovarian tissues. Further, the expression pattern of reported miRNAs was homogenous in majority of cases examined. These studies clearly indicate that aberrant expression of miRNAs may have a clinical relevance.

2.2 Cervical cancer

Cervical cancer (CC) is another common gynecologic malignancy in US [5] (Table 2). Several factors, such as environmental, genetic, epigenetic and viral (HPV) infection are believed to be the common etiological causes for cervical carcinogenesis. Growing evidence suggests that miRNAs exhibit a special expression pattern in CC patients, compared to normal women. Using hybridization arrays, Chen *et al.* examined the expression of 1,450 miRNAs in cervical carcinoma vs. normal cervical tissue [14]. They identified 89 differentially expressed miRNAs; sixty-two miRNAs were more abundantly expressed and twenty-seven miRNAs exhibited down-regulated expression. Furthermore, miRNAs with up-regulated expression in CC tissues were also readily detectable in serum. Some of the common miRNAs exhibiting higher levels in serum and tissue specimens were miR-1246, miR-20a, miR-2392, miR-3147, miR-3162-5p and miR-4484 [14]. Lee *et al.* observed altered expression of 70 miRNAs in cervical carcinomas [15]. These included 68 over-expressed and two down-regulated miRNAs. Gocze *et al.* performed miRNA profiling of primary human CC samples and detected significantly high levels of miR-203, miR-27a,

miR-196a, miR-34a, miR-155, miR-221 and miR-21 in cervical carcinoma, irrespective of clinical grading and HPV status [16]. Moreover, overexpression of miR-34a, miR-196a, miR-27a, miR-221 and miR-21 was found to be the specific signature for HPV-positive cervical carcinomas. Wilting *et al.* identified differential expression of 106 miRNAs during the consecutive stages of CC development [17]. Twenty-seven miRNAs showed early transiently altered expression in high-grade precancerous lesions (CIN2-3) lesions only. Late altered expression of forty-six miRNAs was seen in squamous cell carcinomas and thirty-three miRNAs were continuously altered in both high-grade precancerous lesions and squamous cell carcinomas.

Recently, Nagamitsu *et al.* examined the miRNA expression profile in serum specimen from CC patients by miRCURY LNA microRNA array [18]. Their data suggested that 6 of 1,223 miRNAs were increased >3.0-folds in CC patients, as compared to healthy subjects.miR-1290 was identified to be significantly higher in 45 CC samples. Sharma and coworkers identified novel miRNA signatures in HPV-mediated cervical carcinogenesis in Indian women [19]. They identified 100 differentially expressed miRNAs in pre-cancerous cervix (70 up-regulated and 30 down-regulated miRNAs) and 383 differentially expressed miRNAs in CC (350 up-regulated and 33 down-regulated miRNAs). Further, 182 miRNAs were differentially expressed in HPV-16/18-positive vs. HPV-negative CC cell lines. Several novel miRNAs, namely miR-500, miR-505, miR-711, miR-888 and miR-892b were also discovered in pre-cancerous and CC cases in Indian population [19]. Sequencing data by Jia *et al.* on serum specimens from CC patients vs. healthy controls revealed twelve miRNAs specific to CC, suggesting their use as a promising fingerprint for CC [20]. Li *et al.* performed a meta-analysis of 27 studies that consisted of 943 normal and 1,132 cancer samples [21]. 195 miRNAs were elevated and 96 found to be down-regulated in CC tissues, compared to normal cervical specimens (Table 1). Thus, miRNAs, being highly deregulated in CC, may play role in their pathobiology.

2.3 Endometrial cancer

Endometrial cancer is the most frequently diagnosed GC [5] (Table 2). A number of studies have looked at the miRNA profiles in EC using tumor tissues and other fluidic samples with a goal to identify disease-specific biomarkers. From serum samples of 46 patients with EC, and twenty-eight women without a history of cancer, miRNA profiling was performed using qRT-PCR, and miR-186, miR-222, and miR-223 were identified to be highly elevated [22]. Only miR-204 was expressed at low levels in EC patients. Similarly, another group identified forty-seven differentially expressed miRNAs in EC vs healthy individuals [23]. Of these, twenty-six miRNAs were down-regulated and twenty-one highly expressed. Eight miRNAs were selected and their expression examined in 58 type-IEC patients. miR-141, miR-200a and miR-205 were up-regulated while miR-143 and miR-145 were found to be down-regulated.

For the identification of miRNA signature for endometrial adenocarcinoma, a study identified 112 novel miRNAs specific to endometrial adenocarcinoma, among which miR-182 and miR-183 were highly expressed [24]. In ten pairs of EC and adjacent non cancer endometrium, miRNA expression profiling revealed the elevated level of 17 miRNAs

and reduced levels of 6 miRNAs [25]. From tissue and plasma samples of 77 EC and 45 healthy controls, expression profiling of 866 human miRNAs was performed. Study revealed a distinct pattern of 21 miRNAs in EC specimens. Expression pattern of several miRNAs was found to be associated with International Federation of Gynecology and Obstetrics (FIGO) stage, grade, relapse and nodal metastases. Furthermore, as compared to single miRNAs, the miRNA signatures from tissue and EC plasma specimens could efficiently classify EC with higher accuracy. miR-92a/miR-205/miR-410 and miR-92a/miR-410 was the proposed miRNA signature for tumor tissue, and miR-9/miR-1228 and miR-9/miR-92 was identified to be the plasma-specific miRNA signature of EC [26]. Similar to this, another study reported that subtypes of EC exhibit a distinct miRNA pattern [27]. A specific miRNA signature could distinguish tumor from normal specimens, and miRNA profile differed between type I or II tumors. Working on the similar line, miRNA profiling of grade 1–2 EC suggested specific miRNAs to be an efficient tool for surgical staging in early-stage EC. Significantly low levels of miR-375, miR-184, miR-34c-5p, miR-34c-3p and miR-34b-5p in the primary tumor of EC, with positive lymph nodes, were detected. Women with high miR-375 or reduced expression of miR-184 were more likely to have positive lymph node [28].

Altogether, these studies suggest that miRNAs are dysregulated in GCs. They impact the development and progression of GCs and could be helpful in the effective clinical management of the disease.

3 Biological significance of miRNAs in gynecologic cancers

miRNAs regulate a number of genes with diverse physiological roles. Consequently, the effects of miRNAs are apparent on many biological functions. Some of the better studied biological effects of miRNAs are on cell growth, proliferation, migration, invasion and metastasis. These effects are discussed in next few subsections.

3.1 Cell proliferation, survival and stemness

The effects of miRNAs on the proliferation and growth of cells representing GCs are very well studied. Such effects are often the very first biological effects investigated. Over last several years, a number of publications have detailed the loss or gain of expression of miRNAs in OC, CC and EC, with the resulting impact on growth, proliferation and apoptosis. Due to the enormous number of such reports, a detailed discussion on all of these miRNAs and their target genes is beyond the scope of this article. However, a comprehensive list is provided as Table 3. While some miRNAs have been shown to correlate with increased cell proliferation and growth in CC [29–42], EC [43–49] and OC [50–57], others have been associated with reduced proliferation and/or induced apoptosis in CC [58–88], EC [89–97] and OC [98–144]. As evident, miRNAs have been reported to target a number of genes, mostly mutually exclusive, leading to their effects on cancer cell proliferation.

The miRNAs that induce proliferation of GCs often do so by either targeted inhibition of tumor suppressor genes or the activation of oncogenes. A few examples of such regulation are miRNAs-mediated regulations of tumor suppressors p53 and PTEN. *p53* is a very well

characterized tumor suppressor gene [145]. In an early report on the role of miRNAs in OC cells' proliferation, miR-34b and miR-34/c were reported to be significantly down-regulated (12-folds) as a consequence of p53 inactivation [146]. The two miRNAs, cooperatively, reduced proliferation, as well as anchorage-independent cell growth, thus mediating p53 effects. miR-31 is another miRNA that is associated with p53 pathway, particularly in serous OCs [147], and has anti-proliferative properties [126]. In a latter study, miR-34a was also reported to be a negative regulator of OC proliferation, and its action was shown to be mediated through its regulation of AXL [148]. P53 pathway has been shown to be affected by miRNAs in CC cells as well. TP53INP1 (tumor protein p53-induced nuclear protein 1), a p53 target gene, was shown responsible for proliferation-inhibitory role of miR-17 [59]. PTEN is another classical tumor-suppressor [149]. It is a target of miR-21 [150, 151], miR-130a [152], miR-222 [153] in CC cells; a target of miR-200 [154, 155], miR-205 [47, 156], miR-429 [155] in EC cells and a target of miR-21 [157], miR-106a [158], miR-205 [159], miR-214 [160] and miR-630 [161] in OC. miR-21 induces OC cell proliferation through its targeting of PTEN [157] as well as PDCD4 [162]. PDCD4 has also been identified as a target of miR-21 in HeLa CC cells, responsible for miR-21-induced cell proliferation [163]

miRNAs do not just regulate tumor suppressors. They affect oncogenic signals and signaling pathways as well. NF-κB signaling, for instance, is a target of miR-9 [164]. miR-9 is frequently down-regulated in OC and its overexpression in OC cells can down-regulate NF-κB, resulting in reduced proliferation. The NF-κB-miRNA interactions are further supported by a study in serous OC cells, which observed shorter survival of OC patients with high expression of NF-κB [165]. NF-κB repressed miR-134 expression, resulting in increased expression of its target TAB1, and chemoresistance. In CC cells, NF-κB positively regulates miR-130a by binding to its promoter [152]. miR-130a inhibits PTEN resulting in increased proliferation and growth of OC cells. A role of IKK-β in miRNA regulation of NF-κB has been demonstrated in CC cells. miR-429 represses its target IKK-β which leads to down-regulation of NF-κB, reduced proliferation and increased apoptosis [166]. A number of other pro-survival pathways are also affected by miRNAs. miR-491 induces apoptosis by targeting EGFR which leads to inhibition of Akt and MAPK pathways [167]. This results in BIM accumulation and the inhibition of Bcl-xl. EGFR family is also targeted by tumor suppressor miRNAs, such as, miR-133a in CC [67], miR-125b in EC [92] and miR-133b in OC cells [110]. miR-15a and miR-16 regulate OC cell proliferation by targeting oncogenic Bmi-1 [168].

The 'stemness' of distinct sub-populations of cancer cells is their ability to self-renew and maintain tumors by producing new cancer cells [169]. Such 'cancer stem cells (CSCs)' are known to be involved in cancer metastasis and resistance to therapies. As such, a role of miRNAs in determining the stemness of GCs has also been evaluated. In a recent study [170], the OC cells with stem cell-like properties were reported to express active STAT3 signaling with a mechanistic involvement of miR-92a in the regulation of wnt signaling antagonist DKK1. The miR-92a-STAT3-mediated stemness was shown to be important for chemoresistance. Wnt signaling is also targeted by miR-1207, a miRNA that promotes stemness in OC cells [171]. In another study on OC [172], miR-34a and miR-137 were observed to be important for stemness, as determined by their role in sphere formation and

invasion. These suppressor miRNAs were down-regulated in OC, resulting in de-repression of their target Snail. Snail promoted invasion and sphere formation by inducing EMT. Low levels of miR-34a and miR-137 correlated with poor survival of OC patients [172].

miRNAs have been investigated for their effects on GC cells with expression of specific stem cells markers. In an early report on the topic [173], miR-200a was observed to be down-regulated in CD133/1-positive OC stem cells. ZEB2, the target of miR-200a, influenced invasion of CSCs by inhibiting e-cadherin. Later, another member of the miR-200 family, miR-200c, was shown to regulate stemness in OC [174]. miR-200c was reported to be down-regulated in CD117/CD44-positive ovarian CSCs with resulting increased expression of ZEB1 and vimentin. Low levels of miR-200c correlated with increased colony formation and invasion *in vitro* and increased pulmonary metastases *in vivo*. A few other miRNAs have also been shown to negatively regulate GC stemness. miR-98 inhibits the stemness of ovarian CSCs by targeting EZH2 [175] while miR-134 inhibits ovarian CSCs (CD44/CD133-positive) by targeting RAB27A [176] and endometrial CSCs by targeting POGLUT1 (protein O-glucosyltrasferase 1) [177]. miR-136 has recently been reported to target Notch-3 oncogene and the OC stemness [178]. The effects of miR-136 are evident on CSC phenotype and paclitaxel resistance of OC cells, as over-expression of this miRNA re-sensitizes OC cells to paclitaxel. miR-106a has a distinct effect on GC stemness. In SKOV3 OC cells, over-expression of miR-106a was reported to result in increased CD24/CD133-positive stem cell populations [179]. These studies suggest a correlation between miRNA expression, CSC markers and the resulting effects on CSC-mediated resistance to therapies and metastases. Evidently, a majority of such studies have focused on OC and it remains to be seen if miRNAs can similarly stemness of other gynecological malignancies as well.

3.2 Invasion and metastasis

Invasion of cancer cells into surrounding tissues, and their metastases to distant organs, account for a majority of cancer-associated deaths. Therefore, there has been a wide interest in understanding the ability of miRNAs to regulate the process of invasion and metastases, with possible implications in therapy. Studies have revealed the potential of different miRNAs to either inhibit or induce invasion and/or metastasis of different GCs (Table 3). For example, miR-126 inhibits invasion of EC cells [180]. miR-34a also inhibits invasion, but via differing mechanisms in different cancer cells. In EC cells, it suppresses L1CAM [181] while Notch signaling is its target in CC cells [182]. miR-218 has two different targets within CC cells, focal adhesion pathways [183] and survivin [184], which it regulates to mediate effects on invasion. miR-183 targets MMP3 to inhibit invasion of CC cells [185] while miR-375 inhibits invasion by targeting transcription factor SP1 [186]. miR-205 [187] promotes invasion of EC cells and miR-346 promotes migration and invasion of CC cells by positively regulating AGO2 (argonaute 2) [188].

As discussed above, PTEN and PDCD4 play a role in miRNAs-regulated cancer cell proliferation. miR-21-targeting of PTEN [157] and PDCD4 [162] also affects the invasive potential of OC cells. In addition, PTEN mediates miR-17 effects [189] while PDCD4 is implicated in miR-182-mediated invasion of ovarian carcinomas [190]. Other miRNAs that

regulate invasion of GCs are miR-124 [191], miR-335 [192], miR-339 [193], miR-130b [194] and miR-181 [195]. miR-182 seems to be important for OC metastasis because its inhibition was shown to result in significantly reduced tumor burden, local invasion and distant metastasis in an *in vivo* orthotopic model of serous ovarian carcinoma [196]. miR-22 is a potential metastasis-suppressing miRNA in OC cells with putative regulation of several pro-metastatic genes [197]. miR-204 is another metastasis-suppressor miRNA that plays a role in regulation of OC metastasis through its target, brain-derived neurotrophic factor (BDNF) [198]. miR-138 also associates negatively with OC cells' invasion and metastasis [199]. Its suppressive action is believed to involve SOX4 (SRY-related high mobility group box 4) and HIF-1α (hypoxia-inducible factor-1 α). HIF-1α is also a target of miR-199a [200]. Expression of miR-373 inversely correlates with clinical stage and histological grade of epithelial OCs, and it target is the oncogenic Rab22a [201].

EMT is an important mechanism that plays a key role in invasion and metastasis of cancer cells. A number of miRNAs have been demonstrated to regulate EMT, thereby playing a role in the regulation of invasion and metastasis. miR-200 family, a known family of tumor suppressor miRNAs with well characterized role in EMT of cancer cells [202], has been implicated in EMT of OC cells [203, 204] as well as CC cells [205, 206]. Another member of this family, miR-429, has also been shown to reverse EMT [207]. miR-200a's role in suppressing OC invasion has been attributed to its ability to target CD133/1-positive OC stem cells [173] while the ability of miR-200c to inhibit metastasis has been linked to down-regulation of mesenchymal markers vimentin/ZEB1 and up-regulation of epithelial marker e-cadherin in CD117 and CD44-positive OC stem cells [174].

EMT is also regulated by several other miRNAs, with implications on migration and invasion, in CC, EC and OC cells [172, 208–220]. miR-181a mediates TGF-β-mediated EMT in a smad7-dependent manner and its expression correlates with poor outcome and shorter time to recurrence in patients with epithelial OC [221]. In HeLa and SiHa CC cells, smad7 is a target of miR-519d, an oncogenic miRNA that promotes metastasis [222]. Tumor suppressor let-7a targets smad4 to suppress TGF-β-mediated proliferation of CC cells [223]. In EC cells, smad3 is targeted by miR-23a to modulate TGF-β-mediated EMT [224]. miR-29b [225] and miR-30d [226] inhibit TGF-β-mediated EMT. Through their targets, Id-1 (inhibitor of DNA binding 1) and snail, respectively, they modulate TGF-β-mediated EMT in ovarian cancer cells.

3.3 Modulation of tumor microenvironment

A role of tumor microenvironment in GCs has been realized [227, 228] and the exact mechanism is being explored. In a study that compared normal fibroblasts vs. cancer-associated fibroblasts (CAFs), an important component of TME, miR-148a was found to be significantly down-regulated in 15 of 16 patients-derived CAFs [229]. Consistent with the tumor-suppressive function of this miRNA, conditioned media from CAFs inhibited the migration of multiple EC cell lines. Wnt signaling was shown to be affected by this down-regulation of miR-148a. Since, wnt signaling is known to be important for TME, especially the stromal compartment [230], deregulated miR-148 in CAFs provides a mechanism for role of miRNAs in TME-guided tumorigenesis. Mitra *et al.* compared the miRNA profile of

primary CAFs and adjacent normal fibroblasts in OC patients, and they also performed miRNA profiling in induced CAFs established from normal fibroblasts upon co-culture with tumor cells and normal fibroblasts [231]. They identified miR-214 and miR-31 to be down-regulated and miR-155 up-regulated in CAFs. Furthermore, re-expression of miR-214 and miR-31, and inhibition of miR-155, could revert the CAF phenotype to normal fibroblasts. This clearly indicates a direct role of miRNAs in reversible conversion of normal fibroblasts into CAFs.

In view of the low-oxygen hypoxic conditions in TME, HIF-1α's expression and role has been a subject of interest in TME [232]. Regulation of HIF-1α by miR-199a, with involvement of dynamin 2 and lysloxidase, is believed to play an important role in metastasis of OC cells under hypoxic condition in the TME [200]. Another target of hypoxia-responsive miR-199a is c-met [233]. Reduced levels of miR-199a in TME hypoxic conditions can lead to increased c-met, with resulting activation of Akt pathway and the increased proliferation and invasiveness. In a 3-dimensional culture model of OC TME, an essential role of miR-193b has been demonstrated wherein miR-193b is down-regulated through a direct interaction of OC cells with the mesothelial cells in the microenvironment [234]. Suppression of miR-193b results in de-repression of its target uPA (urokinase-type plasminogen activator), a well-known tumor-associated protease that is involved in invasion and metastases of various human cancers [235]. This activation of uPA results in increased invasion of OC cells into the omentum in an *in vivo* mouse xenograft model as well the human omental pieces *ex vivo* [234].

As an indirect evidence of regulation of TME by miRNAs, hedgehog signaling is regulated by miR-506 in CC cells [236]. Hedgehog signaling is an important modulator of TME where it plays a critical role by creating a niche that favors cancer cells growth, chemoresistance and metastasis [237]. Further, lysophosphatidic acid (LPA), a mitogenic lipid present within the ovarian TME, has been reported to induce the expression of miR-30c-2* [238]. Expression of this miRNA is also affected by epidermal growth factor and the platelet-derived growth factor. This miRNA, affected by tumor microenvironment, seems to counter cell growth by targeting oncogenic BCL9, suggesting a complex regulatory mechanism in cancer cells. Using a preclinical mouse model, it has been demonstrated that delivery of immunostimulatory miR-155 specifically to tumor-associated leukocytes can re-program immunological control of metastatic ovarian cancers [239]. Thus, there are multiple evidences in support of a role of miRNAs in TME.

3.4 Chemoresistance mechanisms

Resistance to chemotherapies i.e. chemoresistance, is another characteristic of cancer cells responsible for making this disease particularly lethal. There are reports on a role of miRNAs in determining response to chemotherapies in GCs [240] (Table 4). Cisplatin and paclitaxel are two drugs that have been studied in detail in GCs, with regards to a role of miRNAs in determining sensitivity and/or acquisition of resistance. The results vary from mere exploration of expression status in sensitive vs. resistant cells to more mechanistic explorations.

In addition its role in cancer cell proliferation, invasion and metastasis, PTEN plays a role in cancer drug resistance as well [241]. miR-93 was identified as a regulator of PTEN/Akt signaling pathway [242]. It directly targeted PTEN to regulate apoptosis and the sensitivity to cisplatin [242]. In a study that investigated miRNA profiles of sensitive vs. cisplatin-resistant OC cells SKOV3, miR-130a was observed to be up-regulated in the resistant cells [243]. miR-130a was, similarly, found elevated in cisplatin-resistant OC cells A2780 as well, compared to the parental cells [244]. Interestingly, PTEN was determined to be a target of this miRNA in both these studies [243, 244]. In addition, miR-130a could inhibit MDR1 [243, 244] and NRP1 (neuropilin 1) [245], which suggests that this miRNA can influence multidrug resistance.

The phenomenon of EMT is known to play a role in acquired resistance to therapy. miR-186 was shown to affect EMT and the resulting cisplatin resistance of OC cells through its target Twist 1 [246]. miR-115 has been reported to reverse cisplatin resistance in CC cells by reversing EMT [247]. In addition to influencing EMT, as discussed the preceding sub-section, miR-200 family can also determine the response to paclitaxel-based therapy, which suggests a possible role as biomarker of response to such therapy [248, 249]. Restoration of miR-200c has been linked to enhanced sensitivity to paclitaxel [250]. Let-7a, another tumor suppressor miRNA that belongs to let-7 family, has also been proposed as a potential biomarker for determining response to paclitaxel [251]. With the objective of delivering let-7i specifically to OC cells, let-7i was combined with MUC1 aptamer [252]. Once delivered, let-7i was observed to down-regulate cell cycle-associated factors, resulting in reversal of paclitaxel resistance. miR-506 is another microRNA that negatively regulates EMT and the resulting chemoresistance of OC cells [253]. Because of its inverse connection with EMT, it was found to associate with favorable response to therapy and overall progression-free survival in an analysis that looked at two independent cohorts of epithelial OC patients with combined sample size of 598 patients [253]. The results were confirmed *in vivo* where miR-506 sensitized cells to cisplatin treatment. miR-25 has been shown to reverse EMT leading to sensitization to cisplatin in HeLa and CaSki CC cells [254].

In a study that compared paclitaxel-sensitive and the derived paclitaxel-resistant KFr13 cells, miR-31 was found to be down-regulated in the resistant cells [255]. miR-31's over-expression resulted in reduced MET, which was proposed to be the mediator of miR-31 effects on paclitaxel sensitivity. Further proof of a role of miR-31 in OC cells' acquired resistance to chemotherapy was provided in a latter study that observed elevated STMN1 (stathmin 1) levels in tissue samples from OC patients with resistance to taxanes, compared to samples from taxane-responsive patients [256]. Comparison of taxane-sensitive vs. resistant OC cells confirmed the increased STMN1 levels in resistant cells, and also revealed a regulation of STMN1 by miR-31. miRNA profiling of formalin-fixed paraffin-embedded OC patient samples helped list a number of up-and down-regulated miRNAs, among which miR-9 was shortlisted as a down-regulated miRNA with possible implications in survival of OC patients [257].

let-7e [258], miR-29 [259], miR-128 [260], miR-136 [261], miR-155 [262], miR-199a [263], miR-216b [264], miR-449a [265], miR-489 [266], miR-595 [267], miR-634 [268] and miR-770 [269] inversely correlate with cisplatin resistance in OC while miR-218 [270, 271]

increases sensitivity to cisplatin in CC cells. miR-21 [272, 273], miR-125b [274], miR-214 [160], miR-224 [275], miR-376c [276] and miR-509 [277] induce cisplatin resistance in OC. A number of other miRNAs, such as miR-106a [278, 279], miR-130b [280], miR-134 [281], miR-145 [282], miR-149 [283], miR-186 [284], miR-197 [285], miR-429 [286], miR-433 [287], miR-490 [288] and miR-591 [278] have been linked to paclitaxel and/or cisplatin resistance in OC. miR-125a [289], miR-224 [290] and miR-375 [291, 292] expression has been linked with paclitaxel resistance in CC cells. Interestingly, although a reduced expression of miR-31 was observed to correlate with paclitaxel resistance [255], its over-expression was reported to drive cisplatin resistance [293].

4 Clinical Significance of miRNAs in gynecologic cancers

The discovery of miRNAs and recent knowledge on their role in gynecological cancer pathobiology has created substantial opportunities for translating the miRNA research into clinical settings. Furthermore, data from emerging studies clearly highlight the clinical significance of these miRNAs in the diagnosis and prognosis of gynecologic malignancies. In the sections below, we have described the implication of these miRNAs as potential diagnostic and prognostic biomarkers.

4.1 Tools for early and differential diagnosis

For the successful treatment of any cancer, early diagnosis is critical. Unfortunately, after several years of research, no major improvements have been made towards the early detection and screening of the GCs. The human epididymis protein 4 (HE4), is an important biomarker for gynecologic malignancies [22, 294], but its sensitivity in patients has been reported as a possible limiting factor [295]. CA125 is another biomarker for gynecologic malignancies, but several factors hinder its implication to be used as specific biomarker [296]. For example, higher levels of serum CA125 are also reported to be associated with pregnancy, menstruation and endometriosis [297]. Even though it has been documented that HE4 has better diagnostic performance than CA125 for early stage diagnosis of EC [298], follow-up studies are highly warranted for identification of novel biomarkers that could serve as superior diagnostic biomarker for this malignancy. Recently miRNAs have gained significant attention as novel diagnostic markers.

miRNAs have the potential to screen/identify cancer patients from healthy individuals, suggesting that the inclusion of these miRNAs along with the current diagnostic markers in combination or alone may yield improved diagnosis and early detection of gynecologic malignancies (Table 5). In this direction, a recent study identified miR-222, miR-223, miR-186, and miR-204 to be the potent miRNAs for the diagnostics of EC [22]. This study also suggested a positive correlation between HE4 levels with miR-222 and miR-223, and a negatively correlation with miR-204. Further, serum miR-204 and HE4 were shown to possess best diagnostic performance in the discrimination of patients with EC vs healthy controls. In the confirmed OC patients, Resnick *et al.* observed that the level of conventional used biomarker CA125 was very low, but a specific miRNAs subset; miR-21, miR-92 and miR-93, was highly elevated in OC patients suggesting the implication of these miRNAs in disease diagnosis with high precision [12]. Earlier studies have reported the overexpression

of miR-944 in several gynecological malignancies, while its clinical significance remained largely unknown [49]. Zuberi *et al.* observed that miR-200a, miR-200b and miR-200c levels were significantly higher in OC, as compared to normal controls [299]. The area under curve (AUC) of receiver operating characteristic (ROC) further suggested that miR-200a and miR-200c could be used as an efficient diagnostic tool. Based on ROC and logistic regression analyses, Zheng *et al.* proposed a diagnostic miRNA panel [300]. Let-7f and miR-205 together were found to provide high diagnostic accuracy for OC, particularly for stage I tumors. The accuracy of detection was further improved when these two miRNAs were combined with CA-125. Moreover, Zheng and coworkers also reported significantly higher level of miR-483-5p in stage III and IV patients as compared to patients with stages I and II [300].

Calura *et al.* identified miRNAs that could be used as diagnostic markers [301]. These miRNAs could specifically discriminate clear cell and mucinous histotypes of OC-higher expression of miR-30a and miR-30a* was specific to clear cell carcinoma while that of miR-192/194 was specific to mucinous histotype. Jia and coworkers identified a miRNA fingerprint for EC detection [302]. This fingerprint/panel included 4 serum miRNAs; miR-222, miR-223, miR-186 and miR-204. The AUC curve of this miRNA signature was remarkably higher than that of CA-125. In 104 EC tissue samples, Torres *et al.* identified several miRNAs to be altered [26]. miRNA signatures miR-92a/miR-205/miR-410 and miR-92a/miR-410 could efficiently classify tumor tissues with higher accuracy, as compared to single miRNAs. miRNA signatures from plasma i.e. miR-9/miR-92a and miR-9/miR-1228, were able to classify the plasma samples of EC patients with high accuracy. Their study thus suggested that these miRNA signatures hold a great promise to be used as promising biomarkers for early detection of EC. A recent study by Coimbra and coworkers found that the expression levels miR-203 and of ΔNp63 mRNA positively correlate with each other in CC tissues, and could serve as a promising tool for the screening of CC [303]. Liu *et al.* suggested the use of miR-196 as a diagnostic marker based on their observation that serum levels of miR-196a are elevated in CC patients as well as in cervical intraepithelial neoplasia (CIN) [304]. Altogether, these reports underscore the potential of miRNAs to be used as valuable tools for discriminating GCs from normal cases and classifying the tumor stage and grade, either alone, or in combination with other biomarkers.

4.2 Predictive and prognostic biomarkers

Recent studies have revealed that the levels of miRNAs are associated with the prognosis of gynecologic malignancies. He *et al.* compared the levels of miR-944 in sixty-eight EC tissues vs. twenty normal endometrial specimens [49]. They identified miR-944 to be consistently up-regulated in EC tissues, and clinicopathological studies suggested high level of miR-944 association with FIGO stages and pathology classification of EC. Further, Kaplan-Meier analysis suggested that patients exhibiting high miR-944 have a shorter survival time. Zuberi *et al.* examined the association of miR-200a, miR-200b and miR-200c with clinicopathological factors and progression of OC [299]. They identified an association of miR-200a and miR-200c with disease progression. miR-200a alone was associated with tumor stage and histology, while high level of miR-200c in patients was associated with lymph node metastasis [299].

Zhai and coworkers reported miR-194 to be remarkably decreased in EC, which correlated with the cancer stage [305]. The decreased expression of miR-194 also associated with poor prognosis. Zheng and coworkers performed a study on 300 patients with OC, and found significantly reduced levels of let-7f in OC patients, compared to healthy controls, suggesting low levels of let-7f to be predictive of poor prognosis [300]. Down-regulation of miR-497 in CC was reported by Luo and colleagues [306]. Their study identified a correlation of miR-497 levels with FIGO stage and lymph node metastases. Moreover, based on multivariate cox analysis, decreased miR-497 expression was demonstrated to associate with poor prognosis of CC. miR-181a-1 has been reported to be over-expressed in various malignancies and its role in the carcinogenesis has also been documented. He *et al.* observed high expression of miR-181a in type I and type II EC [307]. Interestingly, the higher expression of miR-181a was seen in type II EC, rather than type I EC, suggesting that miR-181a could serve as a novel biomarker for EC. Shapira *et al.* [308] examined miRNA levels in the plasma samples of pre-surgery vs. follow-up OC patients. They identified a special signature of five different miRNAs in women with short overall survival, as compared to those exhibiting long overall survival. With aim of identifying miRNAs in plasma for predicting response to treatment and outcome, Halvorsen and coworkers performed miRNA profiling in plasma of ovarian cancer patients with different histology, grade, and FIGO stages [309]. Of 754 unique miRNAs identified, decreased miR-1274a, miR-200b and miR-141 levels were significantly associated with better survival. Low miR-1274a correlated with therapeutic outcome while miR-200c was associated with prolonged progression free survival when treated with bevacizumab, as compared to standard therapeutic regimen [309].

Torres and coworkers also identified a special miRNA signature in EC that associated with FIGO stage, grade, relapse and nodal metastases [26]. Signatures consisting of miR-200a and miR-205 could predict the relapse with high accuracy. Moreover, miRNA signatures from tissues i.e. miR-1228/miR-200c/miR-429 and miR-1228/miR-429 were independent prognostic markers of overall and progression-free survival respectively. Wilczynski *et al.* observed that elevated miR-205 expression was associated with better overall survival, thus suggesting its potential clinical utility as a prognostic marker of EC [310]. Working on the similar line in advanced OC, Parikh *et al.* observed an association between high expression of miR-181a and shorter recurrence time [221]. Yang *et al.* suggested miR-320 as a potential biomarker of radiosensitivity in CC, based on their observation that this miRNA was considerably low in C33AR cells, a radio-resistant CC cell line [311]. Vecchione *et al.* identified a signature of twenty-three miRNAs associated with chemoresistance [312]. Further analysis demonstrated that miR-484,-642, and-217 could predict the chemoresistance of ovarian tumors. Nam *et al.* identified several miRNAs that could discriminate chemosensitive from chemoresistant cases, and detected significant down-regulation of *miR-199a* and *miR-7039* in the chemoresistant group. They also examined the usefulness of miRNAs for detecting chemoresistant disease, and reported that the down-regulation of miR-199a could be an efficient marker for predicting chemoresistant disease [13]. Using the Kaplan-Meier analysis, a very recent study examined the correlation between serum levels of miR-425-5p and the overall survival of CC patients [313]. The results suggested a positive correlation of miR-425-5p with tumor stage and positive lymph node

metastasis. High serum levels of miR-425-5p were suggested to predict poor survival, and cox proportional hazards risk analysis identified miR-425-5p to be an independent prognostic factor for CC.

A correlation between serum miR-196a levels and the tumor size, grade, lymph node metastasis and FIGO stage was suggested by Liu and coworkers [304]. Based on multivariate analysis, authors reported that higher serum miR-196a levels in CC patients were an independent predictor for poor survival. miR-31 has also been reported to be an independent prognostic factor in CC [314]. Multivariate and cox regression analysis demonstrated that high expression of miR-31 associated with poorer overall survival. Moreover, its correlation with FIGO stages and node metastases was also reported. In a pilot study on the role of miRNAs in the prediction of the drug/treatment sensitivity, Benson and coworkers identified plasma miRNAs that can predict outcomes of a carboplatin with decitabine in platinum-resistant recurrent OC patients [315]. They reported that a decreased circulating miR-148b-5p expression level was associated with longer progression free survival, suggesting its potential as a novel biomarker of therapeutic response. Plasma samples were collected from 33 OC patients and it was observed that patients with no miR-200b variation have longer progression free survival. Also, patients with positive variation had higher risk of disease progression [315]. Together, these studies highlight the significance of miRNAs in the prognostic assessments of gynecological malignancies.

4.3 Next-generation of therapeutics

Results from preclinical studies suggest that miRNAs can be exploited as possible therapeutic weapons against GC. miRNA mimics, miRNA nanoformulations, miRNA masks, miRNA sponges and adenovirus-mediated miRNA delivery systems are now being utilized to achieve the gain or loss of miRNA function. For example, MRX34, a liposomal miR-34 mimic, has been successfully tested as a miRNA-based anticancer drug in human phase I trial in patients with advanced hepatocellular carcinoma, thus, highlighting the feasibility of translating miRNAs into cancer therapy in clinical settings [316]. miR-520d-3p has been identified as a tumor suppressor in OC [317]. Nano-liposomes loaded with miR-520d-3p and EphA2-siRNA exhibited potent anti-tumor effect and greater therapeutic efficacy *in vivo* than any of the single treatment. miR-34 family of miRNAs is frequently down-regulated in OC and often associated with metastatic disease [318]. Replacement therapy of miR-34 in the metastatic SKOV3 ovarian cancer cells could inhibit the tumor cell proliferation and metastatic potential [148]. miR-182 overexpression is known to promote the aggressiveness of OC. Xu *et al.* examined the delivery of anti-miR-182 to an animal model mimicking human OC [196]. It was reported that anti-miR-182 treatment is potent enough to inhibit tumor growth and metastasis. Recently, Dwivedi *et al.* tested miR-15a and miR-16 nanoliposomes, either alone or in combination, in a pre-clinical chemoresistant orthotopic mouse model of OC [319]. Their results demonstrated that combination therapy of miR-15a and miR-16 without cisplatin yielded better therapeutic response as compared to cisplatin treatment. Thus, the advent of miR replacement therapy offers novel ammunition for the treatment of GC.

5 Conclusion and future perspectives

Despite the progress in our understanding of the molecular basis of gynecologic malignancies, no major progress has been made in the improvement of patients' survival. For past several years, microRNAs have established themselves as molecules of interest, with possible implications in diagnosis as well as prognosis of GCs. Some interesting observations have led to promising role of miRNAs in therapy of multiple cancers of gynecological origin. Based on the available and emerging data, miRNAs can possibly impact future therapeutic strategies of carcinomas of cervical, endometrial and ovarian origin. However, before this becomes a reality, our understanding of diverse functionality of miRNAs needs to mature further. miRNAs can target multiple genes, and a single gene can be targeted by multiple miRNAs. Thus, there is certain level of redundancy in miRNA-regulation of genes, which needs to be explored. Further, even after numerous reports on the topic, we do not fully understand the complex nature of miRNA-mediated regulation. As an example, miR-26a was first shown to promote OC proliferation through its suppression of ER-α [320]. Subsequently, it was shown to inhibit proliferation of OC cells through its regulation of CDC6 [321]. In CC model, miR-26a inhibits cell proliferation, migration and invasion *in vitro* and also inhibits tumor growth *in vivo* in a xenograft model [322]. Similarly, miR-31/miR-214/miR-494 (Table 3) and miR-222 [323, 324] have different reported roles in different GCs. Thus, there are conflicting reports on the functionality of a single miRNA within a specific GC as well as across different GCs. While this can possibly be explained by closely related-yet distinct miRNA isotypes and the cell line-specific effects; an outcome of targeting of multiple target genes by the same miRNA, the phenomenon needs to be conclusively understood, if the knowledge gained from these observations is to be translated into therapy. As a first step, it is critical to cross-validate the findings by independent teams of researchers, before reaching conclusions with regards to the functionality of miRNAs. After a successful and definitive understanding of the role that miRNAs play in etiology of GC, will come the question as to how miRNAs or the anti-miRs can be systemically delivered, as part of therapy. The strategies to manipulate miRNA levels in cancer patients need to be developed further because when the results from pre-clinical studies emerge, immediate translation to clinics should be possible for the benefit of millions of patients worldwide hoping for a cure and the end to sufferings.

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Highlights

- miRNAs affect proliferation, survival, metastasis and chemoresistance of gynecological cancers
- miRNAs regulate the tumor microenvironment of gynecological cancers.
- miRNAs are novel diagnostic and prognostic markers for individual gynecological cancers and their subtypes

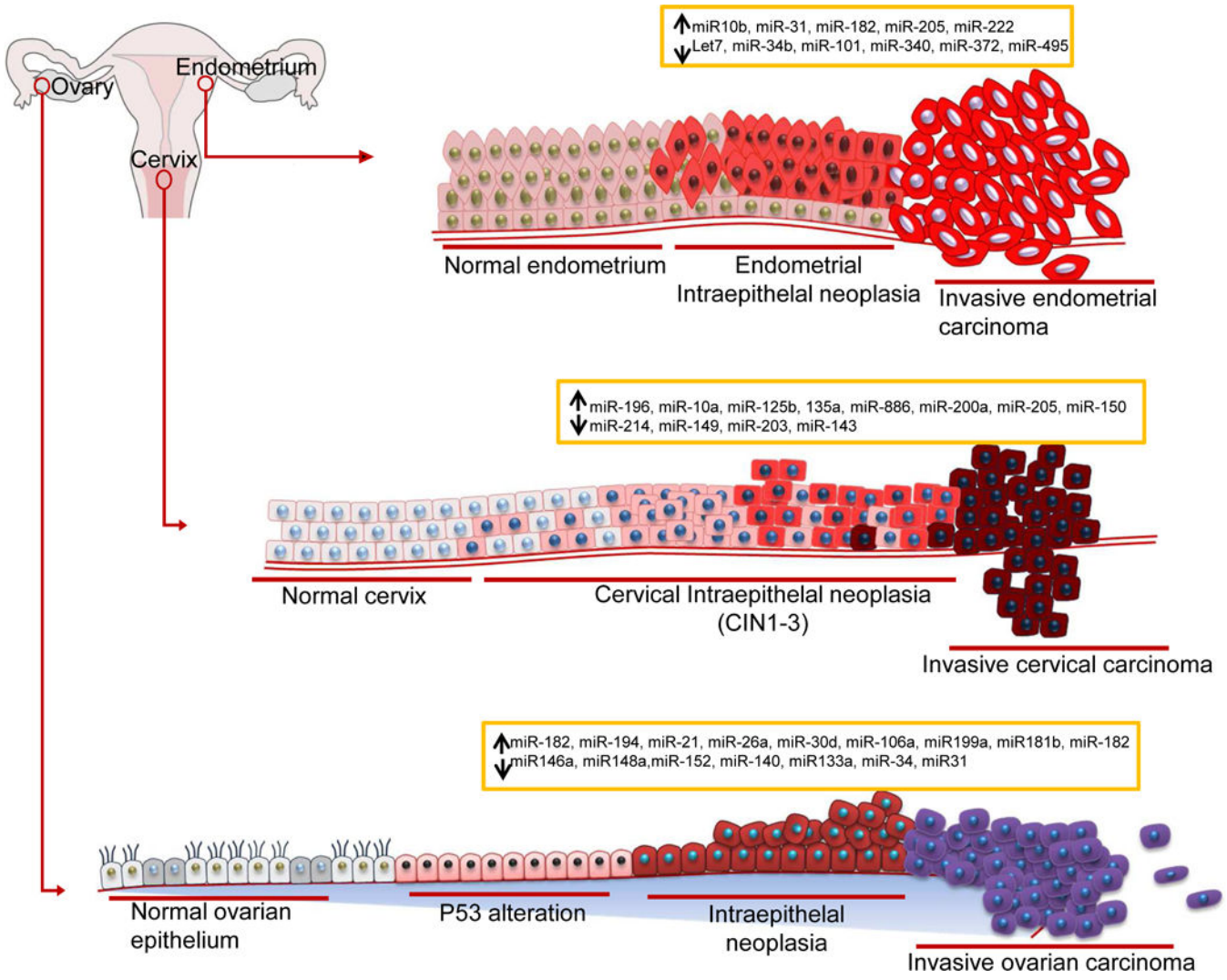

Figure 1.

Table 1

List of aberrantly expressed miRNAs in gynecological cancers.

Up-regulated microRNAs	**Malignancy**	**References**
miR-16, miR-17, miR-20a[a], miR-21[a], miR-23a, miR-23b, miR-27a, miR-29a, miR-30a, miR-92a, miR-93[a], miR-106b, miR-126[a], miR-141[a], miR-144, miR-150, miR-182, miR196a, miR-196b, miR-199a, miR-200a[a], miR-200b, miR-200c[a], miR-375[b], miR-486, miR-449a, miR-499-5p, miR-3613	Ovarian Cancer	[8, 10–13]
miR-9, miR-10a, miR-15b, miR-20a[a], miR-20b, miR-21[a], miR-27a, miR-34a[b], miR-127, miR-133a, miR-133b, miR-141[b], miR-145[b], miR-155, miR-196a, miR-199a*, miR-199a, miR-199b, miR-199-s, miR-200a, miR-203[b], miR-214, miR-221, miR-224, miR-500, miR-505, miR-711, miR-888, miR-892b miR-1246, miR-1290, miR-2392, miR-3147, miR-3162 and miR-4484	Cervical Cancer	[14–16, 18, 19, 21]
miR-9, miR-92a, miR-141, miR-182, miR-183, miR-186, miR-200a, miR-205[a], miR-222, miR-223, miR-410, miR-429, miR-449, miR-1228	Endometrial cancer	[22–26]
Down-regulated microRNAs		
miR-1, miR-99b, miR-127, miR-130b, miR-133a, miR-148a, miR-148b, miR-155, miR-375b, miR-451	Ovarian Cancer	[11–13]
Let-7a, Let-7b, Let-7c, miR-26a, miR-27b, miR-30d, miR-34a[b], miR-100, miR-103b, miR-125a, miR-125b, miR-126, miR-141[b], miR-143[a], miR-145[a,b], miR-149, miR-200b, miR-200c, miR-203[a,b], miR-204, miR-375, miR-451, miR-3185, miR-3196, miR-3960, miR-4324, miR-4467, miR-4488, miR-4525	Cervical Cancer	[14, 15, 21]
miR-99b[a], miR-143, miR-145, miR-193b, miR-204[a]	Endometrial cancer	[22, 23, 25]

[a] miRNAs that have been identified in more than one study

[b] miRNAs that have been reported up-regulated as well as down-regulated within the same gynecological cancer

Table 2

Gynecological Cancers Statistics

Gynecological Cancer	Estimated New Cases	Estimated Deaths
Ovarian Cancer	22,440	14.080
Cervical Cancer	12,820	4,210
Endometrial Cancer	61,380	10,920

Estimates are rounded to the nearest 10, as reported in American Cancer Society's *Cancer Facts & Figures 2017* [5]

Table 3

miRNAs associated with proliferation, survival, stemness, invasion and metastasis of gynecological cancers

miRNA	Gynecological Cancer	Observation	Target	Reference
Let-7	Endometrial	Down-regulated	Aurora-B	[89]
miR-7	Cervical	Down-regulated	XIAP	[58]
miR-9	Ovarian	Down-regulated	NF-κB	[164]
miR-10a	Cervical	Up-regulated	CHL1	[29]
miR-10b	Endometrial	Up-regulated	HOXB3	[43]
miR-15a	Ovarian	Down-regulated	Bmi-1	[168]
miR-16	Ovarian	Down-regulated	Bmi-1	[168]
miR-19a/b	Cervical	Up-regulated	CUL5	[30]
miR-20a	Cervical	Up-regulated	TIMP2/ATG7	[31]
	Ovarian		APP	[50]
miR-21	Cervical	Up-regulated	PTEN	[150]
			PDCD4	[163]
	Ovarian			[162]
		Induces invasion		[157, 162]
miR-22	Ovarian	Inhibits metastasis		[197]
miR-23b	Ovarian	Down-regulated	RUNX2	[98]
			Cyclin G1	[99]
miR-25	Ovarian	Up-regulated	Bim	[51]
miR-26a	Cervical	Down-regulated	PRL-1	[322]
	Ovarian	Up-regulated	ER-α	[320]
		Down-regulated	CDC6	[321]
miR-26b	Ovarian	Down-regulated	OCT4	[100]
miR-27a	Cervical	Up-regulated	B4GALT3	[32]
miR-30d	Ovarian	Up-regulated	–	[52]
miR-31	Endometrial	Up-regulated	YAP1	[44]
	Ovarian	Down-regulated	P53	[126, 147]
miR-34a	Cervical	Inhibits invasion		[182]
		Down-regulated	RIG-I	[60]
			HMGB1	[61]
	Ovarian		AXL	[148]
miR-34b	Endometrial	Down-regulated	MET	[90]
	Ovarian		P53	[146]
miR-34c	Ovarian	Down-regulated	P53	[146]
miR-92a	Cervical	Up-regulated	P21	[34]
			FBXW7	[33]
miR-99a	Ovarian	Down-regulated	FGFR3	[101]
miR-101	Cervical	Down-regulated	COX2	(24289600)

miRNA	Gynecological Cancer	Observation	Target	Reference
	Endometrial		EZH2/MCL-1/FOS	[91]
	Ovarian		EZH2	[102]
			SOCS-2	[103]
miR-106a	Ovarian	Up-regulated	PTEN	[158]
miR-107	Cervical	Down-regulated	MCL1	[63]
miR-125a	Cervical	Down-regulated	ABL2	[65]
			STAT3	[64]
	Ovarian		GALNT14	[104]
miR-125b	Cervical	Down-regulated	PIK3CD	[66]
	Endometrial		ERBB2	[92]
	Ovarian		BCL3	[105]
			EIF4EBP1	[106]
miR-126	Endometrial	Inhibits invasion		[180]
miR-127	Ovarian	Down-regulated	BAG5	[107]
miR-129	Ovarian	Down-regulated	YAP/TAZ	[108]
miR-133a	Cervical	Down-regulated	EGFR	[67]
	Ovarian		IGF1R	[109]
miR-133b	Ovarian	Down-regulated	EGFR	[110]
miR-135a	Ovarian	Down-regulated	HOXA10	[111]
miR-135b	Cervical	Up-regulated	FOXO1	[35]
miR-137	Ovarian	Down-regulated	AEG1	[112]
			XIAP	[114]
miR-138	Cervical	Down-regulated	c-Met	[68]
			hTERT	[69]
	Ovarian	Inhibits invasion and metastasis		[199]
miR-140	Ovarian	Down-regulated	PDGFRA	[115]
miR-142	Cervical	Down-regulated	FZD7	[70]
miR-143	Cervical	Down-regulated	Bcl-2	[71]
	Ovarian	Down-regulated	CTGF	[116]
miR-145	Ovarian	Down-regulated	P7OS6K1	[117, 118]
			MUC1	[118]
			TRIM2	[119]
miR-146a	Ovarian	Down-regulated	SOD2	[120]
miR-148a	Ovarian	Down-regulated	–	[121]
			PDIA3	[122]
			TGFI2	[123]
miR-150	Cervical	Up-regulated	FOXO4	[36]
miR-152	Ovarian	Down-regulated	–	[121]
miR-155	Cervical	Up-regulated	LKB1	[37]

miRNA	Gynecological Cancer	Observation	Target	Reference
miR-181a	Cervical	Down-regulated	GRP78	[72]
	Ovarian	Induces invasion		[221]
miR-181b	Cervical	Up-regulated	AC9	[38]
	Ovarian	Promotes invasion		[195]
miR-182	Endometrial	Up-regulated	TCEAL7	[45]
			Cullin-5	[46]
	Ovarian	Promotes invasion and metastasis		[196]
miR-185	Ovarian	Down-regulated	Six1	[124]
miR-193a	Ovarian	Down-regulated	MCL1	[125]
miR-194	Ovarian	Up-regulated	PTPN12	[53]
miR-195	Cervical	Down-regulated	Cyclin D1a	[73]
			Cyclin D2/MYB	[74, 75]
miR-196a	Cervical	Up-regulated	Netrin 4	[39]
miR-199a	Ovarian	Regulates metastasis in hypoxic tumor microenvironment		[200]
miR-200s	Ovarian	Down-regulated	E-cadherin	[126, 203]
	Ovarian	Inhibits invasion		[173]
	Ovarian	Inhibits metastasis		[174]
miR-203	Cervical	Down-regulated	VEGFA	[76]
miR-205	Cervical	Up-regulated	CYR61/CTGF	[40]
	Endometrial		PTEN	[47]
miR-206	Ovarian	Down-regulated	–	[127]
miR-211	Ovarian	Down-regulated	Cyclin D1/CDK6	[128]
miR-214	Cervical	Down-regulated	GALNT7	[77]
	Ovarian	Up-regulated	PTEN	[160]
miR-218	Cervical	Inhibits invasion		[183, 184]
miR-221	Ovarian	Down-regulated	ARF4	[129]
miR-222	Cervical	Up-regulated	PTEN/p27	[153]
	Endometrial	Up-regulated	ERα	[48]
	Ovarian	Up-regulated	P27	[323]
		Down-regulated	GNAI2	[324]
miR-223	Cervical	Down-regulated	FOXO1	[78]
miR-302a	Ovarian	Down-regulated	SDC1	[130]
miR-302b	Ovarian	Down-regulated	RUNX1	[131]
miR-328	Cervical	Down-regulated	TCF7L2	[79]
miR-331	Cervical	Down-regulated	NRP2	[80]
miR-335	Ovarian	Inhibits invasion		[192]
miR-338	Ovarian	Down-regulated	RUNX2	[132]
			SOX4	[133]
miR-340	Endometrial	Down-regulated	–	[93]

miRNA	Gynecological Cancer	Observation	Target	Reference
miR-342	Cervical	Down-regulated	FOXM1	[81]
miR-346	Cervical	Promotes invasion		[188]
miR-362	Cervical	Down-regulated	SIX1	[82]
miR-372	Cervical	Down-regulated	CDK2/cyclin A1	[83]
	Endometrial		RhoC	[94]
miR-373	Ovarian	Negative regulates invasion and metastasis		[201]
miR-375	Cervical	Inhibits migration and invasion		[186]
miR-376a	Ovarian	Up-regulated	–	[54]
miR-376c	Cervical	Down-regulated	BMI1	[84]
miR-383	Ovarian	Down-regulated	Caspase-2	[134]
			LDHA	[135]
miR-421	Cervical	Down-regulated	Bcl-xL	[85]
miR-448	Ovarian	Down-regulated	CXCL12	[136]
miR-449a	Endometrial	Down-regulated	CDC25A	[95]
miR-486	Cervical	Down-regulated	ECM1	[86]
miR-490	Endometrial	Down-regulated	TGFα	[96]
	Ovarian		CDK1	[137]
miR-494	Cervical	Up-regulated	PTEN	[41]
	Ovarian	Down-regulated	c-Myc	[138]
			FGFR2	[139]
miR-495	Endometrial	Down-regulated	FOXC1	[97]
miR-497	Ovarian	Down-regulated	PAX2	[140]
miR-498	Ovarian	Down-regulated	FOXO3	[141]
miR-506	Ovarian	Down-regulated	CDK4/6	[142]
miR-519d	Ovarian	Down-regulated	XIAP	[143]
	Cervical	Promotes metastasis		[222]
miR-543	Cervical	Up-regulated	BRIP1	[42]
miR-572	Ovarian	Up-regulated	SOCS1/p21	[55]
			PPP2R2C	[56]
miR-630	Ovarian	Up-regulated	PTEN	[161]
miR-634	Cervical	Down-regulated	mTOR	[87]
miR-708	Ovarian	Induced by glucocorticoids, reduces invasion and metastasis		[325]
miR-744	Cervical	Down-regulated	Bcl-2	[88]
miR-761	Ovarian	Down-regulated	MSI1	[144]
miR-939	Ovarian	Up-regulated	APC2	[57]
miR-944	Endometrial	Up-regulated	CADM2	[49]

AC9: Adenylyl cyclase 9

AEG: Astrocyte elevated gene-1

APC2: Adenomatous polyposis coli 2

APP: Amyloid Precursor Protein

B4GALT3: β-1,4-Galactosyltransferase III

BAG5: Bcl2-associated athanogene 5

BRIP1: BRCA1-interacting protein 1

CADM2: Cell adhesion molecule 2

CDK2: Cyclin-dependent kinase 2

CDK6: Cyclin-dependent kinase 6

COX2: Cyclooxygenase 2

CTGF: Connective tissue growth factor

EGFR: Epidermal growth factor receptor

EZH2: Enhancer of zeste homolog 2

FBXW7: F-box and WD repeat domain-containing 7

FGFR2: Fibroblast growth factor receptor 2

FGFR3: Fibroblast growth factor receptor 3

FZD7: Frizzled 7 receptor

GALNT14: N-acetyl galactosaminyl transferase 14

HMGB1: High mobility group box 1

HOXA10: Homeobox A10

HOXB3: Homeobox B3

IGFR1: Insulin-like growth factor 1 receptor

NRP2: Neuropilin 2

PDGFRA: Platelet-derived growth factor receptor alpha

PDIA3: Protein disulfide isomerase family A, member 3

PIK3CD: Phosphoinositide 3-kinase catalytic subunit delta

PRL-1: Protein tyrosine phosphatase type IVA 1

RhoC: Ras homolog gene family member C

RIG-I: Retinoic acid-inducible gene I

RUNX1: Runt-related transcription factor-1

RUNX2: Runt-related transcription factor-2

SIX1: Sineoculis homeobox homolog 1

SOCS1: Suppressor of cytokine signaling 1

SOD2: superoxide dismutase 2

TAZ: Transcriptional co-activator with PDZ-binding motif

TCEAL7: Transcription elongation factor A-like 7

TGFI2: Transforming growth factor-β-induced 2

XIAP: X-linked inhibitor of apoptosis protein

YAP: Yes-associated protein

Table 4

miRNAs reported to modulate resistance of gynecological cancers to therapy

miRNA	Gynecological Cancer	Role in Chemoresistance	Reference
Let-7a	Ovarian	Biomarker for response to paclitaxel	[251]
Let-7i	Ovarian	Reverses paclitaxel resistance	[252]
miR-9	Ovarian	Down-regulated in paclitaxel-resistant tumor samples	[257]
miR-21	Ovarian	Over-expressed in cisplatin-resistant cells	[272]
miR-29	Ovarian	Down-regulated in cisplatin resistant cells	[259]
miR-31	Ovarian	Down-regulated in paclitaxel resistant cells	[255]
		Over-expressed in cisplatin resistant cells	[293]
miR-93	Ovarian	Targets PTEN and regulates sensitivity to cisplatin	[242]
miR-106a	Ovarian	Expression correlates with paclitaxel resistance	[278]
miR-125b	Ovarian	Induces cisplatin resistance	[274]
miR-130a	Ovarian	Induces cisplatin and multi drug resistance	[243]
miR-130b	Ovarian	Negatively correlates with multidrug resistance	[326]
miR-145	Ovarian	Epigenetically silenced in paclitaxel-resistant cells	[282]
miR-152	Ovarian	Increases sensitivity to cisplatin	[327]
miR-155	Cervical	Reverses EMT and cisplatin resistance	[247]
miR-185	Ovarian	Increases sensitivity to cisplatin	[327]
miR-186	Ovarian	Negative regulator of EMT and resulting cisplatin resistance	[246]
miR-199b	Ovarian	Epigenetically silenced in cisplatin-resistant cells	[328]
miR-200s	Ovarian	Determine response to paclitaxel-based therapy	[248, 250]
miR-214	Ovarian	Induces Cisplatin resistance	[160]
miR-218	Cervical	Increases cisplatin sensitivity	[270, 271]
miR-224	Cervical	Increases paclitaxel sensitivity	[290]
miR-375	Cervical	Up-regulated in paclitaxel resistant cells	[291, 292]
miR-376c	Ovarian	Induces Cisplatin resistance	[276]
miR-497	Ovarian	Hypermethylated in cisplatin resistant cells and tumors	[329]
miR-506	Ovarian	Determines sensitivity to cisplatin by inhibiting EMT	[253]
miR-591	Ovarian	Down-regulated in paclitaxel resistant cells	[278]

Table 5

miRNAs with potential role as diagnostic markers in gynecological cancers

miRNA	Gynecological Cancer	Putative Diagnostic Role	Reference
Let-7f/miR-205	Ovarian	Accurate diagnosis of stage I tumors	[300]
miR-21/miR-92/miR-93	Ovarian	Elevated in patients	[12]
miR-30a	Ovarian	Diagnostic marker for clear cell carcinoma subtype	[301]
miR-92a/miR-205/miR-410	Endometrial	miRNA signature for diagnosis	[26]
miR-192/miR-194	Ovarian	Diagnostic markers for mucinous subtype	[301]
miR-196	Cervical	Elevated serum levels in patients	[304]
miR-200s	Ovarian	Differentially expressed in patients	[299]
miR-203	Cervical	Diagnostic marker	[303]
miR-204	Endometrial	Correlates negatively with diagnostic marker HE4	[22]
miR-222/miR-223	Endometrial	Correlate positively with diagnostic marker HE4	[22]
miR-483	Ovarian	Diagnostic marker for stage III and IV tumors	[300]