Role of microRNAs regulating trophoblast cell function in the pathogenesis of pre-eclampsia (Review)

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Abstract. Pre-eclampsia (PE) is a complicated pregnancy-specific disease and is considered the primary reason for maternal and foetal mortality and morbidity. PE has a multifactorial pathogenesis but the causes of PE remain unclear. The functions of trophoblasts, including differentiation, proliferation, migration, invasion and apoptosis, are essential for successful pregnancy. During the early stages of placental development, trophoblasts are strictly regulated by several molecular pathways; however, an imbalance of these molecular pathways can lead to severe placental lesions and pregnancy complications. Certain microRNAs (miRs) are abnormally expressed in PE, with several miRs involved in the regulation of pregnancy-associated genes. The present review discusses the miRs regulating trophoblast function, how they affect the pathogenesis of PE and evaluating the possibility of miRs in screening, diagnosis and treatment of PE.

Contents

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Abbreviations: PE, pre-eclampsia; miR, microRNA; EV, extracellular vesicle; AUC, area under the curve; dsRNA, double-stranded RNA; IUGR, intrauterine growth restriction; C19MC, chromosome 19 miRNA cluster; C14MC, chromosome 14 miR cluster; circRNA, circular RNA

Key words: miR, pre-eclampsia, trophoblast

1. Introduction

Pre-eclampsia (PE) is a complicated pregnancy-specific disease that is characterized by hypertension (≥140/90 mmHg on at least two occasions ~4 h apart) and impaired function of one or more organs or systems, with proteinuria no longer considered as a symptom of the disease (1). Affecting 3-8% of pregnant people worldwide, PE is considered a leading cause of maternal and foetal mortality and morbidity (2). It can lead to severe multisystem complications such as eclampsia, liver and kidney failure, as well as cerebral haemorrhage. In addition, foetuses can be affected by PE, such as prematurity and intrauterine growth restriction (IUGR) (3). PE is classified as early- (<34 weeks of gestation) and late-onset PE (>34 weeks of gestation) (4). Early-onset PE, accounting for 20% of PE cases, tends to have more serious consequences for the mother and foetus, including IUGR, intrauterine death, premature delivery and placental abruption, while late-onset PE, accounting for 80% of PE cases, is associated with risk factors such as insulin resistance, obesity, chronic hypertension, dyslipidaemia and thrombophilia, but not IUGR (4,5). Women with PE have a 4-fold increased risk of heart failure in later life, a 2-fold increased risk of coronary artery disease and stroke and an increased risk of cardiovascular disease in the offspring (2).

The pathogenesis of PE is attributed to multifactorial causes involving multiple risk factors and mechanisms (1). Nonetheless, the pathogenesis of PE remains unclear and it has been shown that it may be associated with placental dysfunction, an insufficient recast of uterine spiral arterioles, excessive activation of the immune system, damage to vascular endothelial cells, abnormal balance of angiogenic and antiangiogenic factors, as well as genetic factors (6,7). At present, control of gestational hypertension and termination of pregnancy is considered the best available treatment option for PE (1,8). Several interventions, such as calcium and low-dose aspirin, have been shown to decrease mortality and morbidity in pregnant people at high risk for PE (8). To the best of our knowledge, no single test can reliably predict the risk of

PE, although tests of maternal angiogenic factors have some predictive value, while risk prediction models and biomarkers may be different among different populations (9).

In the human genome, non-coding RNAs (ncRNAs) constitute 98% of the human genome and include microRNAs (miRNAs or miRs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs) (10). ncRNAs are involved in several pathological and physiological processes in the human body such as cell proliferation and adhesion as well as angiogenesis (10). The regulation of ncRNAs alters gene activity, thereby regulating gene expression and transcription, as well as chromatin structure, epigenetic memory and protein translation (11). Epigenetic changes, in particular altered expression of certain miRs, may play key roles in placental-related disease such as PE and IUGR, which cause changes in placental gene expression, mediate downstream effects and promote development of placental dysfunction (12). Some lncRNAs and circRNAs inhibit the function of miRs by binding to other miRs, thereby acting as miR sponges (13). As a large family of ncRNAs, the association between miRs and PE has been studied extensively in the field of perinatal medicine. Several miRs are differentially expressed in PE (14-16). Dysregulation of miRs is also found in endometriosis, where they cause differential expression of endometrial stem/progenitor cells (17). As a key component of the placenta, dysfunction of trophoblasts is crucial to the development of PE (5). The present review summarizes the function of miRs regulating trophoblast and discusses their application in the treatment of PE.

2. Biological characteristics and production of miRs

miRs are short-sequence and single-stranded RNAs with a stem-loop structure that do not encode proteins. They are 19-25 nucleotides in length and bind to the 3'-untranslated regions of mRNAs to regulate mRNA translation or direct shear of mRNAs at the post-transcriptional level (18). The regulation of miRs is complex because a miR can target multiple genes, while one gene can be the target of several miRs (19). miRs are involved in almost all life processes. For example, miRs participate in cell function regulation and serve critical roles in the occurrence and development of disease (19). In addition, miRs exhibit high stability in extracellular fluids, which provides a foundation for identifying miRs as biomarkers (20).

Under the action of polymerase II, DNA is transcribed into a primary miR with a hairpin structure and a polyadenylic acid tail composed of several thousand nucleotides (21). Following cutting by the RNase III Drosha and its cofactor DiGeorge syndrome critical region 8, a stem-loop-like miR pre-cursor miR (pre-miR) is formed, which is ~70 nucleotides in length (18). Ras-related nuclear protein GTPase and exportin-5 transport pre-miR from the nucleus to the cytoplasm (22). Under the shearing action of the nuclease Dicer and transactivation response element RNA-binding protein or the protein activator of the interferon-induced protein kinase, pre-miR is processed to form a double-stranded RNA (dsRNA) with a length of ~22 nucleotides (23). Under the action of argonaute protein, one strand of dsRNA can be guided into the RNA-induced silencing complex to become a mature single-stranded miR that regulates genes, while the other strand is degraded (24). The biosynthesis of miRs is shown in Fig. 1. The absence of Dicer protein in the miRNA biogenesis pathway can lead to severe defects in reproductive function. For example, defects in the Dicer protein damage the corpus luteum and lead to female rat infertility, while defects of embryonic Dicer lead to early embryonic death associated with the loss of mouse stem cells (25). In addition, mutations in mouse argonaute-2 protein cause placental development defects or foetal death during the second trimester of pregnancy (26).

3. miRs are expressed in PE

It has been estimated that ~400 miRs exist in trophoblasts of the normal human placenta (27). miRs are expressed in specific chromosomal regions and are regulated by the same promoter such as placenta-derived chromosome 19 miR cluster (C19MC; containing 54 different miRs with functions in the placenta and reproductive system during the third trimester of pregnancy) and chromosome 14 miR cluster (C14MC; containing 34 miRs with high expression in placental tissue and embryos during early pregnancy) (27). Decreased expression of C19MC miRs (miR-515-5p, miR-518b, miR-518f, miR-519d and miR-520h) has been reported in the placenta of patients with PE, with these miRs regulating the immune system and inflammatory response (28). However, there is no significant difference in C19MC miRs in PE complicated by IUGR compared with PE alone (29). miR-378a-5p, which is located on C14MC, is downregulated in the placenta of patients with PE and it regulates expression of Nodal (a transforming growth factor) to inhibit trophoblast proliferation and migration and induce trophoblast apoptosis (30). In mouse models, several miRs identified as key immunomodulators in other tissue are differentially expressed in early pregnancy, such as miR-146a, miR-155 and miR-223, suggesting that they are involved in the maternal adaptation to pregnancy (25,31). Furthermore, miRs that exert angiogenic and antiapoptotic properties are primarily expressed in the placenta during early pregnancy, while miRs that promote cell differentiation are strongly expressed in the placenta during late pregnancy (32). Therefore, miRs promote successful pregnancy and regulate differentiation and development of the placenta and foetus during pregnancy. An imbalance of miRs leads to pregnancy-related disorders such as gestational hypertension and diabetes, IUGR and prematurity (33).

The expression of miRs in the placenta is influenced by changes in pregnancy, which includes genetic, environmental and immunological factors; thus, miR expression profiles change dynamically (34). For example, let-7d is downregulated in the circulation of pregnant patients with PE, but there is no difference compared with patients with normal pregnancy, while let-7d expression is upregulated in the placenta, indicating that apoptosis is critical in the control of trophoblasts (33,35). Furthermore, expression miR-584 and miR-17 (both play important roles in malignant tumour progression) is inconsistent in different studies (36,37). The levels of six miRs (miR-1, miR-328, miR-363, miR-377, miR-500 and miR-584), which are downregulated in the placenta of patients with PE, are not statistically different in sera from patients with PE and healthy pregnancy (38). PE may have multiple predisposing factors and placental pathology,, which may be the reason for the inconsistent regulation of some miRs in the pathogenesis of PE (36). For example, miR expression in the

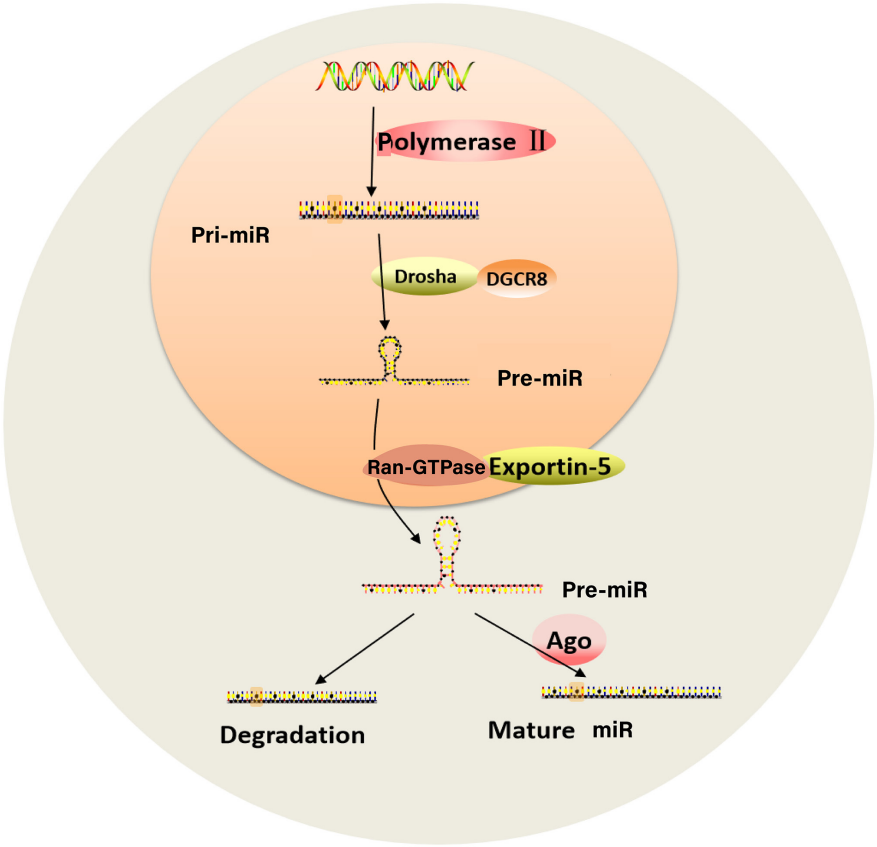

Figure 1. Biosynthesis of miRs. Under the action of Ppolymerase II, DNA is transcribed into a pri-miR. Following cutting by the RNase III Drosha and its cofactor DGCR8, pre-miR is formed. Ran-GTPase and exportin-5 transport pre-miR from the nucleus to the cytoplasm where it is processed to form dsRNA. Then, one strand of the dsRNA becomes a mature single-stranded miR that regulates genes, while the other strand is degraded. miR, microRNA; DGCR8, DiGeorge syndrome critical region 8; Ran-GTPase, Ras-related nuclear protein GTPase; dsRNA, double strand RNA; pri-, primary; Ago, argonaute protein.

placenta is influenced by maternal nutritional status, obesity and pregnancy body mass index (39).

4. miRs regulate the activity of trophoblasts

Placental development includes differentiation, invasion and migration of trophoblasts as well as the remodelling of uterine spiral arteries. During the early stages of placental development, dynamic replacement of trophoblasts is strictly regulated by several molecular pathways; however, an imbalance of these molecular pathways leads to severe placental lesions and pregnancy complications (40). The upregulation of miR-370-3p can inhibit trophoblast proliferation, migration and invasion while promoting apoptosis (41). miR-326 targets paired box 8 via the Hippo pathway to inhibit trophoblast proliferation migration and invasion (42). In addition, expression of let-7b is significantly decreased in the placenta of patients with PE. Let-7b adversely affects the function of trophoblasts via the ERK1/2 signalling pathway and it inhibits cell proliferation and invasion, promotes cell apoptosis and autophagy, as well as increasing TNF-α expression in trophoblasts of patients with PE (43). On the other hand, miR-134 inhibits infiltration of trophoblasts by targeting ITGB1 (44). Migration and invasion of trophoblasts are similar to metastatic behaviour of tumour cells. Certain miRs that are abnormally expressed in malignant tumours are also differentially expressed in PE. For example, miR-21, which affects tumour cell proliferation and viability, inhibits invasion and promotes apoptosis of trophoblasts (45). miRs can also combine with other ncRNAs to play a role in regulating downstream target molecules. The lncRNA SNHG5 affects expression of miRs by adsorbing miRs and upregulating the transcription of the secreted protein acidic and cysteine-rich gene, thereby inhibiting autophagy in trophoblasts of patients with PE (46). miRs that have been reported to regulate trophoblasts are listed in Table I (47-58).

The differentiation and proliferation of trophoblasts in the placenta are inseparable from the blood supply. The development of blood vessels in the placenta requires vascular factors such as VEGF, placenta growth factor, angiopoietin and soluble endothelin. The current theory is that an imbalance between angiogenic factors and antiangiogenic factors may be the cause of PE (59). Studies have reported that these angiogenic genes are targeted by multiple miRs, which are associated with pathogenesis of PE (33,36); among them, 127 miRs have been demonstrated to be associated with PE and VGEF-A can be targeted by ten different miRs, while VEGF-B is targeted by nine different miRs (36), suggesting that miRs may promote the development of PE by influencing synthesis and secretion of vascular factors.

5. miRs regulate the stress response of trophoblasts

The failure of uterine spiral artery remodelling leads to placental ischemia and hypoxia, which stimulates maternal

Table I. Differentially expressed miRs associated with pre-eclampsia trophoblast.

First author/s, year	miR	Source	Expression	Target	Effect	(Refs.)
Yuan *et al*, 2020	miR-16	Placenta	Up	Notch2	Inhibits proliferation, migration, invasion and promotes apoptosis of trophoblast	(47)
Wang *et al*, 2019; Zhang *et al*, 2012	miR-210	Placenta	Up	Notch1, Ephrin-A3, homeobox -A9	Inhibits proliferation, migration, invasion and promotes apoptosis of trophoblast	(48,49)
Xiaobo *et al*, 2019	miR-149-5p	Placenta	Up	Endoglin	Inhibits proliferation, migration, invasion and promotes apoptosis of trophoblast	(50)
Liu *et al*, 2021	miR-126	Placenta	Up	VCAM-1	Inhibits invasion of trophoblast	(51)
Ali *et al*, 2021	miR-16	Maternal serum	Up	TP53	Promotes apoptosis of trophoblast	(52)
Shi *et al*, 2019	miR-454	Placenta	Down	Activin receptor-like kinase 7	Proliferation, invasion of trophoblast	(53)
Liu *et al*, 2021	miR-126	Placenta	Up	VCAM-1	Inhibits invasion of trophoblast	(51)
Lai and Yu, 2020	miR-183	Placenta	Up	FOXP1, G protein subunit γ7	Inhibits proliferation, invasion, and angiogenesis of trophoblast	(54)
Wang *et al*, 2020	miR-132	Placenta	Up	Death associated protein kinase 1	Proliferation, migration, invasion and apoptosis	(55)
Wang *et al*, 2019	miR-141, miR-200a	Placenta, maternal serum	Up	Endocrine gland-derived-VEGF	Inhibits proliferation, migration, invasion and promotes apoptosis of trophoblast	(56)
Yang and Meng, 2020	miR-215-5p	Placenta	Up	CDC6	Inhibits migration and invasion of trophoblast	(57)
Ni *et al*, 2021	miR-95-5p	Placenta	Up	Low-density lipoprotein receptor-related protein 6	Inhibits migration and invasion of trophoblast	(58)

VCAM-1, vascular endothelial cell adhesion molecule-1; miR, microRNA.

immune cells. Under these conditions, active T lymphocytes increase production of inflammatory cytokines such as TNF-α and interleukin-6 (60). TNF-α decreases transcription of nitric oxide synthase and increases production of endothelin-1, a potent vasoconstrictor (60). In addition, placental ischemia triggers oxidative stress characterized by production of excessive reactive oxygen species in the endoplasmic reticulum and cell chambers, leading to protein and DNA damage (61). In response to chronic inflammatory stimulation, miR-195 expression is downregulated, which inhibits mitochondrial energy production by targeting flavin adenine dinucleotide-dependent oxidoreductase domain-containing protein 1 and pyruvate dehydrogenase phosphatase regulatory subunit coding genes, leading to apoptosis of trophoblasts under oxidative stress (62). Furthermore, plasma miR-210 levels in patients with mild or severe PE are ~4- and 10-fold higher than those in healthy individuals, respectively (63). In patients with PE and trophoblasts cultured under hypoxic conditions, upregulated miR-210 expression in the placenta and plasma is associated with cell migration and vascular remodelling (64). In addition, the upregulated miR-210 expression in patients with PE may also mediate mitochondrial damage via iron-sulphur cluster scaffold homolog, thereby promoting pathogenesis of PE (65). Collectively, these mechanisms induce chronic inflammation in the placenta. Inflammation promotes apoptosis and disrupts migration of trophoblasts, affects formation of placental blood vessels and aggravates the immune response. The role of miRs in the pathogenesis of PE is shown in Fig. 2.

6. Applications of miRs in PE

PE cause great harm to the foetus (IUGR, intrauterine death, prematurity and placental abruption) (36). In addition, symptoms of PE are usually detected after 20 weeks of gestation; thus, it is difficult to diagnose PE before this time (1). Therefore, PE prediction in the first trimester may help to treat the complications associated with PE. In this regard, it is essential to explore molecular mechanisms of PE and to identify the early biomarkers of PE. The dysregulation of miRs in the placenta not only affects the function of the placenta, these miRs may also affect maternal physiology and foetal growth and development (2).

A recent study reported that miR-363 is associated with early-onset PE and can be used as a potential biomarker to

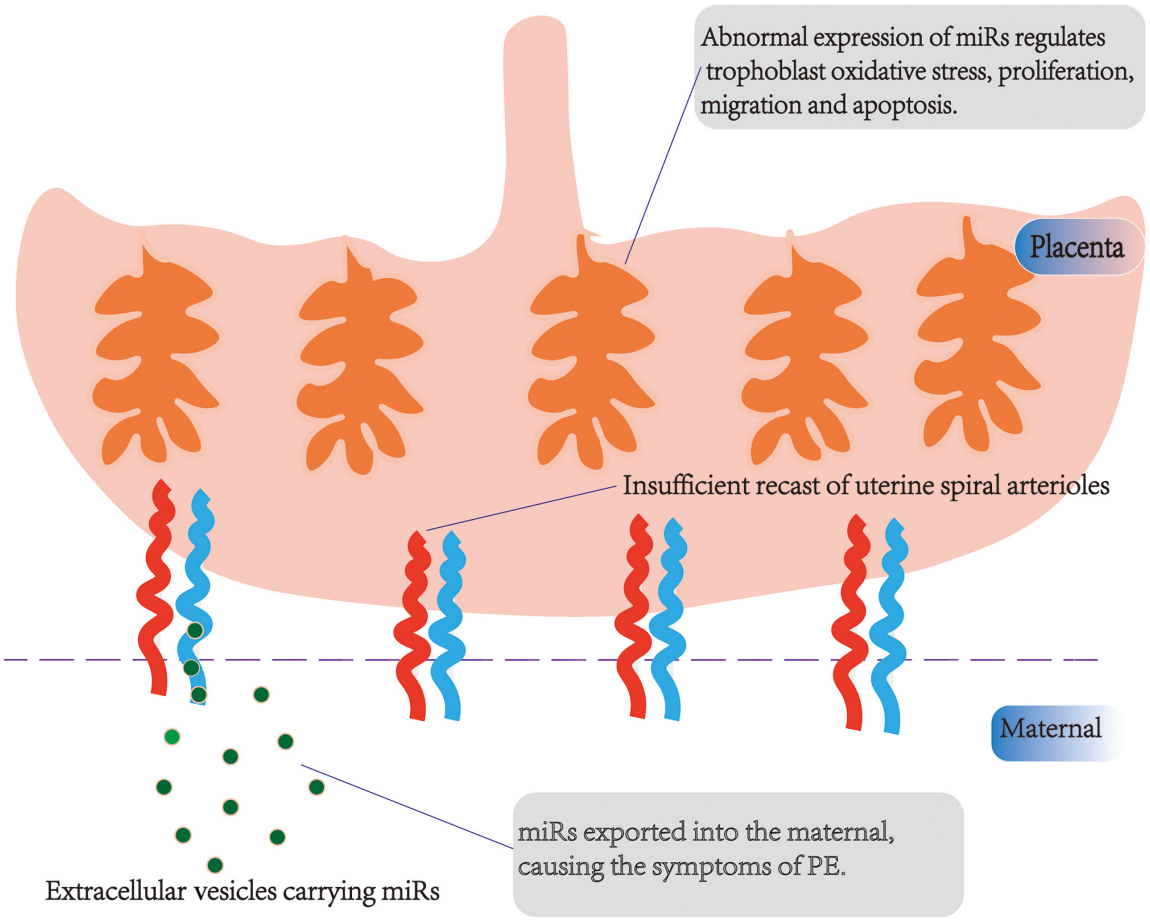

Figure 2. Roles of miRs in pathogenesis of pre-eclampsia. miRs participate in the oxidative stress of trophoblasts while inhibiting proliferation and invasion and promoting apoptosis. miRs are present in extracellular vesicles and exported into the maternal blood, causing the symptoms of preeclampsia. miR, microRNA.

diagnose early- and late-onset PE (66). Gan *et al* (67) demonstrated that the areas under the curves (AUCs) of miR-210 and miR-155, which are upregulated in the serum of patients with PE, are 0.750 and 0.703, respectively. Furthermore, miR-152 (AUC=0.94), miR-183 (AUC=0.97) and miR-210 (AUC=0.93) in maternal serum at 20-24 weeks of gestation predict PE (33). In maternal serum of patients with early stage of pregnancy, Hromadnikova *et al* (29) reported that miR-517-5p, a placenta-specific C19MC miR, has the best predictive performance for PE, with a sensitivity of 42.9% and a specificity of 86.2%, but that circulating C19MC miR has no predictive value for IUGR. A clinical trial demonstrated that serum miRs in early pregnancy do not have a predictive value for early PE (68). By using miR microarray and quantitative polymerase chain reaction analysis, Luque *et al* (68) reported no differences in 754 miRs in the serum of 31 early-onset patients with PE with early pregnancy compared with the serum of 44 patients with normal early pregnancies. A previous study found that miRs in maternal serum in early pregnancy predict late-onset PE and miscarriage (AUC=0.90), but the authors used a miR panel of 30 miRs, which increases the cost of screening (69). It has been established that miRs form a huge network of ncRNAs. For example, miR-210 is differentially expressed in a variety of cancers and cardiovascular and inflammatory diseases, which renders miRs non-specific biomarkers of PE (2,70,71). Furthermore, PE is a disease involving multiple factors and mechanisms, which makes it difficult to identify highly specific miRs in PE (33). At the same time, due to the complex regulatory characteristics of miRs, similar situations may exist for other diseases (33). Therefore, further studies are required in the future.

miRs are present in extracellular vesicles (EVs), indicating that they can be exported into the maternal blood and *in vitro* experiments have reported that EVs in pregnant patients with severe PE impair endothelial cell function (72,73). Development of EV inhibitors based on characteristics of EVs and the pathway targets of miRs may serve an important role in prevention and treatment of PE. Thus, miRs have potential for disease diagnosis and treatment and it may be possible to prevent and treat PE at the miR level. At the same time, artificial intelligence and machine learning techniques, which can find important connections between data items in diverse data sets, can be used to identify miRs as improved biomarkers of diseases with potential in the diagnosis and treatment of other disease (74).

7. Summary

An increasing number of miRs have been reported to be involved in the pathogenesis of PE (2). miRs play important roles

in the regulation of genes in the pathogenesis of PE, thereby participating in oxidative stress of trophoblasts while inhibiting proliferation and invasion and promoting apoptosis (75). The identification of biomarkers of PE has been actively researched in perinatal medicine (76). However, to the best of our knowledge, current research on miRs lacks detail and the roles of miRs in the pathogenesis of PE remain unclear. Highly stable miRs are potential biomarkers and therapeutic targets for PE. However, the pathogenesis of PE, as well as the roles of miRs, are complex and diverse. PE is regulated by different mechanisms and patients exhibit different miR expression profiles (68,76). Therefore, the challenge in molecular medicine is to find a biomarker, or panel of biomarkers, for early diagnosis of PE, as well as individualized prediction and treatment strategies.

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Authors' contributions

YimC designed the study. WN and BW wrote the manuscript. YijC and JL wrote, reviewed and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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