

BMJ Open Predictive value of miR-210 as a novel biomarker for pre-eclampsia: a systematic review protocol

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To cite: Nikuei P, Davoodian N, Tahamtan I, *et al.* Predictive value of miR-210 as a novel biomarker for pre-eclampsia: a systematic review protocol. *BMJ Open* 2016;**6**:e011920. doi:10.1136/bmjopen-2016-011920

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2016-011920>).

Received 15 March 2016
Revised 13 August 2016
Accepted 1 September 2016

ABSTRACT

Introduction: Pre-eclampsia (PE) is a serious condition affecting 3–5% of all pregnancies worldwide. However, underlying molecular pathogenesis of this disease has largely remained unknown. Recently, several studies have indicated the possibility role of microRNAs, especially miR-210, in the aetiology of PE. The aim of this systematic review is to assess the possible role of miR-210 as a novel biomarker for the prediction of PE.

Methods and analysis: Using a combination of mesh terms 'preeclampsia', 'microRNA' and their equivalents, an electronic search will be performed for all observational studies (cross sectional, case-control and cohort) in PubMed, Web of Science, Scopus, Embase, Cochrane, LILACS and OvidSP MEDLINE from January 2005 to December 2015. Furthermore, other sources are searched, including grey literature, reference lists of relevant primary studies as well as key journals. Study selection, data extraction and quality assessment of studies will be performed independently by 2 reviewers, and any disagreement will be resolved by consensus. If sufficient data are available, it will be combined by either fixed or random effects models. We will investigate the source(s) and degree of heterogeneity using 'Heterogeneity χ^2 ' and I^2 . Heterogeneity would be investigated through either subgroup analysis or metaregression. Stata V.11.1 will be used for data analysis.

Ethics and dissemination: The results of this study are disseminated in peer-reviewed journal articles and academic presentations. Formal ethical approval is not required, since the secondary data will be collected.

Trial registration number: CRD42015032345.

BACKGROUND

Pre-eclampsia (PE) is a human pregnancy-specific disorder characterised by a new onset of hypertension. It affects 3–5% of all pregnancies worldwide and remains as a leading cause of maternal and neonatal mortality and morbidity.¹ Risk factors for PE are obesity, prior hypertension, maternal age, kidney disease, autoimmune diseases and diabetes mellitus.² Although the aetiology of PE is largely unknown, the placenta in

Strengths and limitations of this study

- This systematic review, for the first time, will assess the predictive value of miR-210 in patients with pre-eclampsia.
- Study selection, data extraction and quality assessment of studies will be conducted independently by two reviewers.
- Subgroup analysis or metaregression will be used for investigation of the observed statistical heterogeneity.

general and trophoblast in particular are pre-requisites for the development of this disease. It is characterised by incomplete trophoblast invasion and aberrant spiral arterial remodelling, leading to decreased uteroplacental perfusion, placental ischaemia and hypoxia.³ Diagnostic criteria for PE include the presence of hypertension, developing after 20 weeks of gestation, and the coexistence of one or more of the following new-onset conditions: proteinuria, maternal organ dysfunction and uteroplacental dysfunction.⁴ Early-onset PE is usually defined as PE that develops before 34 weeks of gestation, while late-onset PE develops at or after 34 weeks of gestation.⁵

PE is considered severe when systolic blood pressure is higher than 160 mm Hg or diastolic blood pressure is higher than 110 mm Hg. HELLP syndrome (platelet level <100 000/dL, alanine aminotransferase or aspartate aminotransferase elevation of twofold the upper limit of normal, and haemolysis with elevated lactate dehydrogenase twofold the upper reference limit or >650 IU/L) is severe complications of PE.⁵

Several angiogenic and antiangiogenic factors, including placental growth factor (PlGF), soluble fms-related tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng), have recently been suggested for detection of PE.^{6–9} However, there is controversy over using these factors, as most of them are not



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sensitive or specific enough to be used for clinical diagnosis.^{10–11} Early diagnosis would allow medical management/intervention, resulting in the improvement of outcomes for the mother and fetus.¹² Currently, several studies have identified the expression of microRNAs (miRNAs) in placenta tissue, which may be involved in pregnancy-associated disorders, such as PE.^{12–15}

miRNAs are small non-coding RNAs, playing important roles in regulating gene expression by degradation or translation repression of mRNAs. miRNAs have several biofunctions, including development, differentiation and apoptosis, as well as oncogenesis.¹ Recently, miRNAs have generated great interest as potential novel diagnostic biomarkers for cancer,^{16–17} tissue injury¹⁸ and PE.¹² Aberrant expression of miRNAs has been recently reported in PE placenta and serum.^{13–15 19–22} The most commonly identified placental miRNA in PE is miR-210, which is well known as a hypoxia-responsive miRNA.^{14 23 24} The level of miR-210 increases in response to low oxygen tension in many different cell types, and it is upregulated in hypoxia-associated diseases, such as cancer and PE.^{14 23} Although many researchers have published their data on the predictive value of miR-210 in PE, and have raised concerns about the efficiency of miR-210 as a biomarker, this issue remains questionable.

So far, a few narrative reviews have discussed the role of miR-210 in PE, confirming its involvement in the pathogenesis of this disease.^{1 12 25 26} To the best of our knowledge, a systematic review has not yet been conducted to evaluate the predictive value of miR-210 for PE.

Objectives

The purpose of this systematic review is to evaluate the predictive value of miR-210 in pre-eclamptic patients.

METHODS

This systematic review adheres to the PRISMA-P guidelines.²⁷ The systematic review protocol is registered in 'International Prospective Register for Systematic Reviews' (PROSPERO) and its trial registration number is CRD42015032345.²⁸

Eligibility criteria

Types of studies

All observational studies (cross-sectional, case-control and cohort) will be included if they meet the following criteria: (1) the studies reporting miR-210 expression level in serum, plasma and placenta of women affected to PE; (2) studies describing PE according to ISSHP. However, if a study does not mention the 'PE definition', it will be assessed by authors, and if PE is the outcome of interest, the study will be included; (3) the results on the occurrence of PE should be described by 'means' and 'SD'. Animal studies and review articles are excluded.

Participants

Women who developed PE after 20 weeks of gestation are included in the study. The term healthy pregnant women are considered as controls.

miR-210

miRNAs are a class of non-coding RNA, which negatively regulate gene expression.¹ miR-210 is the most commonly identified placental miRNA found to be upregulated in pre-eclamptic patients. Using microarray and real-time PCR, several studies have reported overexpression of this miRNA in the trophoblast cells under hypoxia condition, which is thought to be one of the important causes of PE.^{14 23 24}

In the current review, studies evaluating the relationship between miR-210 expression level and PE are included.

Outcomes

According to the 'International Society for the Study of Hypertension in Pregnancy' (ISSHP),⁴ PE is defined as: hypertension developing after 20 weeks of gestation and the coexistence of one or more of the following new-onset conditions:

1. Proteinuria
2. Other maternal organ dysfunction:
 - ▶ renal insufficiency (creatinine >90 µmol/L)
 - ▶ liver involvement (elevated transaminases and/or severe right upper quadrant or epigastric pain)
 - ▶ neurological complications (examples include eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, and persistent visual scotomata)
 - ▶ haematological complications (thrombocytopenia, disseminated intravascular coagulation, haemolysis)
3. Uteroplacental dysfunction
4. fetal growth restriction

As definitions and diagnosis criteria for PE may vary, when PE is the outcome of interest, the study will be eligible for inclusion.

Search strategy

With no language restriction, literature search will be performed in PubMed, Web of Science, Scopus, Embase, Cochrane, LILACS and OvidSP MEDLINE, using a combination of mesh terms 'preeclampsia', 'microRNA' and their equivalents, from January 2005 to December 2015. The search strategy for OvidSP MEDLINE is shown in [table 1](#). This search strategy can be modified as required for other electronic databases.

Other resources

Grey literature, reference lists of relevant primary studies as well as key journals will be searched for additional studies.

Table 1 Search strategy used in OvidSP MEDLINE

1	Exp Pre-Eclampsia/
2	Pre-Eclampsia.ti,ab,kw,mp.
3	Pre Eclampsia.ti,ab,kw,mp.
4	Pre-Eclamp*.ti,ab,kw,mp.
5	Preeclamp*.ti,ab,kw,mp.
6	eclamp*.ti,ab,kw,mp.
7	Eclampsia.ti,ab,kw,mp.
8	Preeclampsia.ti,ab,kw,mp.
9	EPH Complex.ti,ab,kw,mp.
10	EPH Gestosis.ti,ab,kw,mp.
11	EPH Toxemias.ti,ab,kw,mp.
12	EPH Toxemia.ti,ab,kw,mp.
13	(Toxemias AND EPH).ti,ab,kw,mp.
14	(Gestosis AND EP).ti,ab,kw,mp.
15	EPH.ti,ab,kw,mp.
16	(Toxemia* AND Pregnancy).ti,ab,kw,mp.
17	Pregnancy Toxemias.ti,ab,kw,mp.
18	Pre-eclamptic toxaemia.ti,ab,kw,mp.
19	Pre-eclamptic toxemia.ti,ab,kw,mp.
20	Preeclamptic.ti,ab,kw,mp
21	1/20 OR
22	hsa miR.ti,ab,kw,mp.
23	micro RNA.ti,ab,kw,mp.
24	miR.ti,ab,kw,mp.
25	miRNA .ti,ab,kw,mp.
26	MIRN.ti,ab,kw,mp.
27	hsa-mir.ti,ab,kw,mp.
28	microRNA.ti,ab,kw,mp.
29	miR.ti,ab,kw,mp.
30	22/29 OR
31	21 AND 30

Data collection and analysis

All retrieved documents will be transferred to EndNote software (X6) and duplicated articles will be removed from the Endnote library. Then, the title and abstract of the found documents will be evaluated to exclude non-relevant studies. Afterward, according to the inclusion and exclusion criteria of this study, the eligibility of the full texts of the remaining articles will be assessed independently by two reviewers. At this step, any disagreement will be resolved by consensus between the two authors.

The required data will be extracted by two reviewers from relevant studies, independently. The data include: (1) setting and study design, (2) author, (3) publication year, (4) type of disease (mild or severe), (5) occurrence time of disease (early or late), (6) mode of delivery (normal vaginal or caesarean), (7) ethnicity, (8) type of sample (placenta or serum), (9) methods used for the evaluation of expression (microarray and real-time PCR), (10) key measures for meta-analysis, including: relative risk, mean difference, standard mean difference and sample size.

If data from the same study are reported in multiple publications, they will be considered as one study. We will also attempt to contact authors of the studies with

possibly relevant but unpublished data. If no response is received from the author(s) of such publications, they will be contacted in the intervals of 15 days for three times. In cases where no responses are received, they will be excluded from the study. Any disagreement will be resolved by consensus between the two authors.

Assessment of methodological quality

Quality assessment of primary studies will be independently conducted according to a modified version of 'Strengthening the Reporting of Observational Studies in Epidemiology' guideline (STROBE), by two reviewers.²⁹ The questions will be answered as yes with 1 point, and no or unclear with zero. After the assessment of each article, its total score will be calculated. Afterward, the studies will be categorised into three levels: low risk, high risk and unclear risk of bias. Disagreements between the two authors will be resolved by consensus.

Statistical analysis and data synthesis

Stata software, V.11.1 (StataCorp LP, College Station, Texas, USA), will be used to analyse the extracted data. The meta-analysis will be used to assess the effectiveness of miR-210 for the prediction of PE. If meta-analysis is not feasible, narrative synthesis may be conducted. The main key measures (sample size, mean difference and standard mean difference) will be combined with fix or random models. Forest plot will be used for graphics. The p value of <0.05 will be interpreted as statistically significant.

Heterogeneity assessment

The source(s) (and degree of heterogeneity will be investigated by 'Heterogeneity χ^2 ' and I^2 . I^2 value <50% will be considered as there is no heterogeneity, while I^2 value higher than 50% shows the existence of source(s) of heterogeneity, which would be investigated through either subgroup analysis or metaregression if sufficient studies were available.²⁷ Likely sources of heterogeneity would be severity of disease (mild or severe), occurrence time of disease (early or late), mode of delivery (normal vaginal or caesarean), ethnicity, type of sample (placenta or serum), primiparity or multiparity and the method (microarray and real-time PCR) used for the expression evaluation.

Assessment of reporting bias

Finally, reporting of publication bias will be assessed by using 'Funnel Plot', 'Begg's and Egger's test' or 'Plot Fill and Trim method'.

DISCUSSION

miRNAs have generated great interest for their potential roles as diagnostic and prognostic biomarkers in various diseases.^{30–32} Recently, several studies have demonstrated the aberrant expression of miRNAs between placenta of

women affected to PE and normal placenta.^{33–35} Findings of these studies suggest miRNA's contribution in the pathogenesis of PE, especially by altering the development of placenta.^{21 33 36} As a sensor of hypoxia, miR-210 has most frequently been identified to be overexpressed in PE.^{14 23 24} It is likely that miR-210 involves in the development of trophoblast cells.^{14 23 24} Moreover, several studies have reported the striking role of miR-210 in repression of trophoblast migration, invasion and angiogenesis.^{3 14 34} Therefore, the dysregulation of this miRNA may be responsible for the limited proliferation and shallow invasion of trophoblast cells as well as the insufficient remodelling of maternal spiral arteries. Based on the aforementioned results, this study will assess the predictive value of miR-210 as a novel biomarker for PE.

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Contributors ND and PN contributed to the study design, initial drafting and data extraction. IT developed the search strategy and revised the manuscript. AAK critically revised the manuscript, and provided important intellectual input. All authors approved the final version of the manuscript for publication.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement This study is a systematic review protocol, assessing miR-210 as a novel biomarker for prediction of pre-eclampsia, from January 2005 to December 2015.

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