Reports of Biochemistry & Molecular Biology
Vol.7, No.1, Oct 2018

Original article

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Assessment of Correlation Between miR-210 Expression and Pre-Eclampsia Risk: A Meta-Analysis

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Abstract

Background: Pre-eclampsia (PE) is a pregnancy disorder characterized by hypertension and proteinuria. The evidence has suggested that microRNAs (miRs) are associated with pre-eclampsia pathogenesis; however, these results are inconsistent. The aim of this study was to assess the association between miR-210 expression and PE risk.
Methods: Previous studies were selected using PubMed, Scopus, MEDLINE, EMBASE, Science Direct, Google Scholar, Directory of Open Access Journals (DOAJ), and Scientific Information Database (SID). This meta-analysis includes 12 studies associated with miR-210 and pre-eclampsia and necessary information was extracted.
Results: The standardized mean differences [(SMD (0.32) 95% CI (014–0.49), p=0.97] and heterogeneity were determined with the chi-square test (Q=3.63 df =11 p= 0.97), which found no heterogeneity between these studies. Additionally, publication bias was evaluated by Egger's and Begg´s tests. Visual inspection of the funnel plot graphically, and statistically with Egger's weighted regression [(p= 0.35) (95% CI -0.90 – 2.29)] and Begg's rank correlation (p= 0.21), found no important publication bias between studies within the meta-analysis.
Conclusions: Our findings suggest that miR-210 contributes to the pathogenesis of PE; therefore, miR-210 could serve as a novel biomarker to predict PE pathophysiology. Further studies are required in this field to characterize the mechanism involved in this process.

Keywords: Meta-analysis, MiR-210, Pre-eclampsia.

Introduction

Pre-eclampsia (PE) is a disorder of pregnancy characterized by hypertension and proteinuria (1). It affects 5-8% of all pregnancies and is the leading cause of maternal and infant morbidity and mortality worldwide (2). The major etiology of PE is unknown, but the disease develops in placenta and trophoblast dysfunction (3, 4). Defects of trophoblast cell function, such as reduced proliferation and aberrant differentiation, are associated with PE (5). Risk factors for PE are prior hypertension, obesity, advanced maternal age, kidney disease, autoimmune diseases, and diabetes mellitus (6). Diagnostic criteria for PE include hypertension developing after 20 weeks of gestation, proteinuria, maternal organ dysfunction, and utero-placental dysfunction (7). Early-onset PE usually develops before 34 weeks of gestation, while late-onset PE is defined as PE that develops after 34 weeks of gestation (8). Expression of some genes is dysregulated during the disease. These genes could be useful as biomarkers and their identification could further our understanding of PE (9). microRNAs (miRNAs) are a class of noncoding RNAs 20-22 nucleotides in length that regulate gene expression through mRNA degradation and translation inhibition (10). These molecules are involved in numerous cellular events including development, differentiation,

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Received: Sep 18, 2017; Accepted: Oct 15, 2017

apoptosis, oncogenesis, hypoxia response, and others (11). One miRNA identified in placentas of pregnant women with PE is miR-210 (12, 13). Recent research revealed that miR-210 is up-regulated in PE patients. In addition, repression of trophoblast cell invasion by miR-210 was reported (14). Therefore, miR-210 could be a potential biomarker for prognosis and diagnosis of PE (15). miR-210, a member of hypoxia-induced miRs, also known as hypoxia-miRs, is ubiquitously expressed in a variety of cells including mammary epithelial and trophoblast cells (16). The extraordinary stability of miRs makes them appropriate diagnostic biomarkers for some diseases. Aberrant miR-210 expression is present not only in solid tumors and harmed organs, but is also secreted into the circulation, allowing detection in plasma (17). To date, no data on the predictive value of miR-210 in PE has been reported; therefore, the aim of this meta-analysis is to assess the predictive value of miR-210 as a novel PE biomarker.

Materials and methods

Meta-analysis search strategy

We searched PubMed, EMBASE, Pro-Quest, Scopus, Google Scholar, MEDLINE, the Directory of Open Access Journals (DOAJ), the Asian Science Citation Index (ASCI), and the Scientific Information Database (SID) for eligible studies in English up to May 2015. The search keywords were (microRNA 210 OR miR-210) AND pre-eclampsia and (placenta miR-210 [ti/ab] AND pre-eclampsia [ti/ab]).

Other resources

Grey literature, conference abstracts, reference lists relevant to inclusion criteria, and key journals were searched for additional studies.

Study inclusion/exclusion criteria

Studies were included if they: 1) were published in English, 2) included pregnant women with pre-eclampsia, or 3) measured levels of miR-210 in plasma and placenta, and excluded if they 1) were about miRNAs other than miR-210 or 2) were review articles or letters, brief reports, abstracts, or comments with limited data.

Data extraction

All studies were surveyed independently by two reviewers. Data extracted from these studies included the authors, country, year of publication, sample, sample size, patient and control ages, systolic and diastolic blood pressures, fold changes in miR-210 expression, miR-210 detection methods, and weeks of gestation.

Table 1. Selected studies and their characteristics.

Author	Country	Year	Sample	Sample size (PE/Con)	Mean Patient Ages	Mean Control Ages	SBP PE (mmHg)	DBP PE (mmHg)	Fold change mir-210	Methods to detect mir-210	Weeks of gestation	QA with STROBE	Ref
Bath LP	USA	2007	Placenta	9/9	28	24	167 (148-190)	105 (84-111)	5.39	qPCR	33	16	(18)
Zhu X	China	2009	Placenta	15/11	31.9	31.8	170±26	111±9	3±0.5	qPCR	37	17	(19)
Kathleen ML	USA	2010	Placenta	7/7	23.8	30	≥140	≥90	2.5	qPCR	31-39	16	(20)
Gunel T	Turkey	2011	Serum	20/20	-	-	-	-	>2	qPCR	26-40	10	(21)
Zhang Y	China	2011	Placenta	15/15	31.6	29.7	173±9	109±7.8	9.49 (7.10-	qPCR	-	18	(14)
Daniel AE	Swedish	2011	Placenta	20/20	32.8	30.4	119.5 (8.1)	76 (6.5)	1.97	qPCR	16	20	(22)
Miami A	Iraq	2012	Placenta	30/50	26.57	28.56	>160	>110	1.89±0.13	qPCR	35-36	15	(23)
Lauren A	USA	2013	Placenta	33/34	25.5	26.2	-	-	>1.6	qPCR	1-12	19	(24)
Peng X	China	2014	Placenta	20/33	30	31	161±17	109±7.8	2.95	qPCR	35-39	17	(25)
Blendi U	Italy	2014	Serum	24/24	34.4	33.7	-	-	3.3 (3.1)	qPCR	12-14	12	(26)
Rongcan L	Canada	2014	Placenta	13/22	29.33	31.72	156.41±12.63	101.30±7.61	-	qPCR	36-40	17	(27)
Qian L	China	2015	Serum	32/32	28.7	28.1	>140	>90	0.93	qPCR	20	17	(28)

Quality assessment

Two reviewers used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to assess the methodological quality of the primary studies(29). Twenty-two questions were asked; each yes answer received one point, and each no or unclear answer received zero points. After each article was assessed, its total score was calculated. The highest quality studies received the highest scores (Table 1, QA with STROBE).

Statistical analysis

We analyzed the data using Mantel-Haenszel fixed effects in meta-analysis. Standardized mean difference (SMD) (Cohen's d) values with 95% confidence intervals (CIs) were calculated using STATA statistical software version 12.0 (STATA Corporation, College Station, TX, USA). The statistical heterogeneity was measured using the Higgins I-square. $P<0.05$ with $I^2>50\%$ was considered representative of significant statistical heterogeneity. Publication bias is a major concern for many meta-analysis studies; three methods were used to assess this. The funnel plots as visuals were calculated. The Begg's rank correlation and the Egger's weighed regression methods were also used to assess publication bias. $P<0.05$ was considered representative of statistically significant publication bias. The meta-analysis was also performed using STATA version 12.0.

Results

Selection of studies

Using the inclusion and exclusion criteria described in Materials and Methods, 12 studies were selected (Fig. 1).

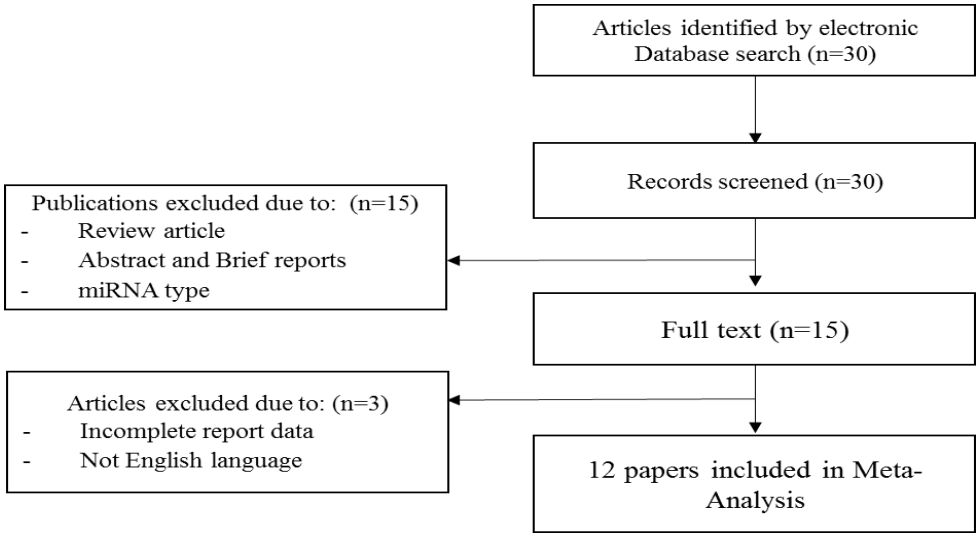


Fig.1. Selection of studies

Study characteristics

We identified 12 PE studies that reported changes in miR-210 levels. Table 1 lists the studies and their characteristics. The PE and control groups included 238 and 277 subjects, respectively. Of these 12 studies, nine used placentas and three used sera. The mean ages in the PE and control groups ranged from 23.8 to 34.4 years. The mean fold miR-210 expression changes in the studies ranged from >1.6 to 9.49-fold. Pre-eclampsia pathology occurred at all gestation times from 1-40 weeks. All the studies used qPCR to measure miR-210 expression (Table 1).

The overall results of miR-210 level and pre-eclampsia risk

Figure 2 (Fig. 2) presents the results of the overall SMD for the correlation between miR-210 levels and PE risk calculated as the mean difference between the intervention and control groups. The overall SMDs were evaluated for miR-210 level [SMD (0.32), 95% CI (0.14 – 0.49), p= 0.97]. The result showed the miR-210 expression level may be predictive and serve as a diagnostic tool for PE. No statistically significant heterogeneity between studies was found using the chi-square test [(Q=3.63 df =11, p= 0.97),

(I^2= 0.0%)] or by visual inspection of the Galbraith plot (Fig. 3). Visual inspection of the funnel plot found no evidence of publication bias (Fig. 4A). Publication bias was also not found using either the Begg's rank correlation (*p*= 0.21) or Egger's weighted regression methods [(*p*= 0.35), 95% CI (-0.90 –2.29)] (Fig. 4B). Taken together, these findings suggest an association between miR-210 expression and PE pathophysiology. Our results indicate that miR-210 could serve as a novel biomarker to predict PE pathophysiology.

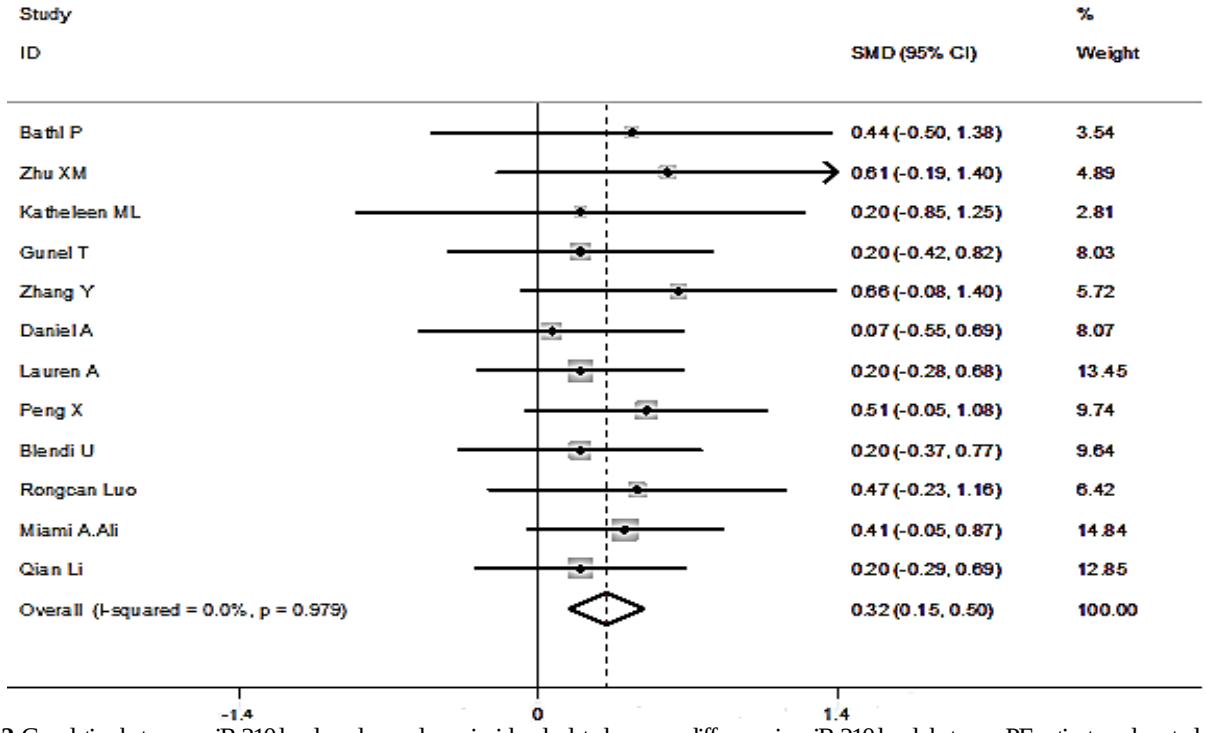


Fig. 2. Correlation between miR-210 levels and pre-eclampsia risk calculated as mean difference in miR-210 levels between PE patients and controls.

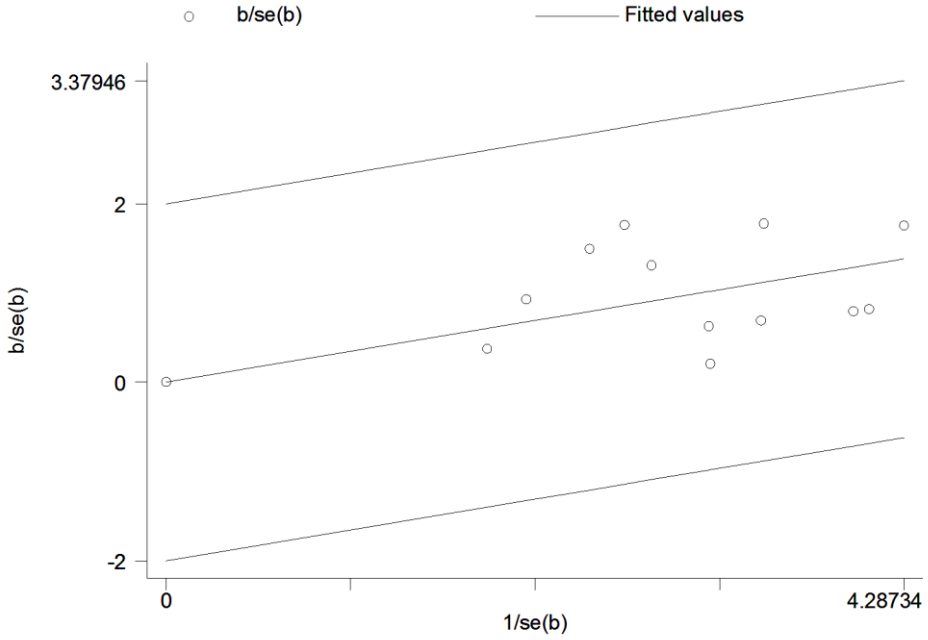
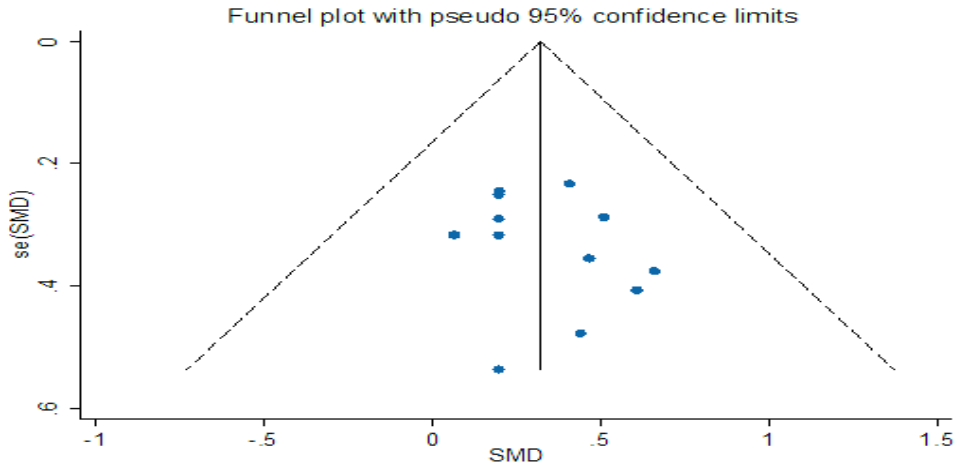


Fig. 3. Heterogeneity analysis with a Galbraith plot. Visual inspection of the Galbraith plot showed no evidence of publication bias. In this plot all the studies (circles) are inside the -2 and +2 lines; therefore, no heterogeneity exists between these studies.

A)



B)

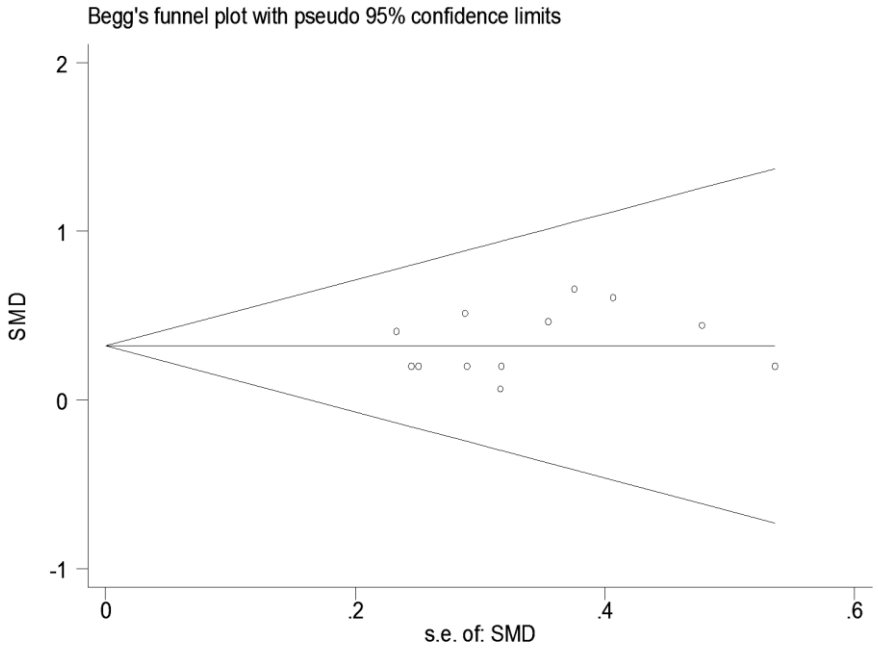


Fig. 4. Publication bias shown graphically (A) as a funnel plot and statistically (B) with the Begg's rank correlation and Egger's weighted regression methods. Visual inspection of the funnel plot and the Begg's rank correlation (p= 0.21) and Egger's weighted regression [(p= 0.35), 95% CI (-0.90 – 2.29)] methods found no publication bias between studies within the meta-analysis.

Discussion

The association between PE and altered miRNA expression suggests the possibility of a functional role for miRNA in this disease. Aberrant miRNA expression has been recently reported in PE patient placentas and sera (30). The most commonly identified placental miRNA in PE is miR-210, which is a hypoxia-responsive miRNA. The aim of this meta-analysis was to investigate a possible association between miR-210 levels and PE. We used 12 studies related to miR-210 and PE. The meta-analysis was performed using a fixed-effect model and no clear heterogeneity was seen. The standardized mean differences [(SMD= 0.32) 95% CI (0.14–0.49)] showed that miR-210 could serve as a novel biomarker to predict PE. Publication bias was not evident using either the Begg's rank correlation or Egger's weighted regression methods, suggesting that the results are correct. These results provide evidence that miR-210 offers promise as a biomarker to predict PE pathophysiology. Pre-eclampsia is characterized by hypertension, proteinuria, and edema in pregnancy (1, 31). Pineless *et al.* screened 157 miRNAs from

patients with PE and small-for-gestational age (SGA) neonates, and controls, and found that miR-210 and miR-182 levels were increased in PE patient placentas. They also showed that a rise in miR-210 expression in maternal plasma may be a predictive biomarker for non-invasive prenatal PE diagnosis (18). Ura *et al.* reported 12 upregulated and seven downregulated miRNAs in PE patient sera, with miR-210 as one of the upregulated miRNAs (26). Zhang Y *et al.* demonstrated that an increase in miR-210 expression inhibits migration and invasion of trophoblast cells and eventually, hypoxia-induced upregulated miR-210 can alter trophoblast behavior (14). MiR-210 is upregulated in hypoxic conditions and high miR-210 expression is a possible modulator of mitochondrial dysfunction during PE. Thus, miR-210 may have a fundamental role in placental mitochondrial function in PE patients (32).

Muralimanoharan *et al.* demonstrated that high miR-210 expression is related to a decrease in mitochondrial respiration, and upregulated reactive oxygen species in PE showed a role for miR-210 in placental dysfunction (33). It was also shown that miR-210 expression can be used to predict PE development 8 to 12 weeks before the clinical onset of symptoms; therefore, miR-210 may be a target in therapeutic strategies for at-risk (24). This meta-analysis provides a comprehensive report regarding the important role of miRNA-210 as a novel biomarker in PE.

Our meta-analysis has several strengths: 1) We obtained the most comprehensive data on the correlation between miR-210 expression and PE risk, 2) our search strategy was highly detailed, spanned multiple databases, and included published data with English language, 3) no evidence of publication bias was found, and 4) the methodological quality of the selected trials was assessed using scaled STROBE guidelines.

Our meta-analysis also has limitations: 1) owing to the small number of studies for specific outcomes of miR-210 we were not able to better evaluation the correlation between miR-210 expression and PE risk. Given this limitation, our findings should be interpreted with caution, and demonstrate the need for detailed future intervention studies with miR-210 levels as primary outcomes.

In conclusion, miR-210 expression differed between PE patients and healthy controls. Further studies are needed to characterize the association between miR-210 and PE. It will be interesting to determine whether the differential miRNA expression profiles in placentas correlate with those in maternal plasma, especially because these may serve as diagnostic markers for PE.

Acknowledgements

This project was supported by the Proteomics Research Center of Shahid Beheshti University of Medical Sciences.

Conflict of interest

The authors declare no conflicts of interest.

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