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Abnormal blood biomarkers in early pregnancy are associated with preeclampsia: a meta-analysis

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ABSTRACT

Objective: Our aim was to evaluate the strength of association between abnormal levels of first trimester maternal blood biomarkers and the risk of preeclampsia.
Study design: We searched MEDLINE, EMBASE and Cochrane databases from inception until April 2013. Studies that assessed the association between any abnormal maternal blood biomarker in the first trimester and preeclampsia were included. Two independent reviewers selected studies, extracted data and assessed the quality. Results were summarized as pooled odds ratios with 95% confidence intervals.
Results: From 1071 citations, we identified 30 studies (65,538 women) for inclusion. Twenty four studies assessed preeclampsia of any onset, 10 studied early onset preeclampsia and seven evaluated late onset preeclampsia (after 34 weeks of gestation). The biomarkers PAPP-A (OR 2.1, 95% CI 1.6, 2.6), PP13 (OR 4.4, 95% CI 2.9, 6.8), sFlt-1 (OR 1.3, 95% CI 2.9, 6.8), pentraxin (OR 5.3, 95% CI 1.9, 15.0) and inhibin-A (OR 3.6, 95% CI 1.7, 7.6) were significantly associated with any preeclampsia. The odds of early onset preeclampsia were significantly increased when the biomarkers PlGF (OR 3.4, 95% CI 1.6, 7.2), PAPP-A (OR 4.8, 95% CI 2.5, 22.5), PP13 (OR 7.5, 95% CI 2.5, 22.5), soluble endoglin (OR 18.5, 95% CI 8.4, 41.0) and inhibin-A (OR 4.1, 95% CI 1.9, 8.8) were abnormal. Two biomarkers, soluble endoglin (OR 2.1, 95% CI 1.9, 2.4) and inhibin-A (OR 1.9, 95% CI 1.4, 2.8) were significantly associated with late onset preeclampsia.
Conclusion: Abnormal maternal blood biomarkers in early pregnancy are significantly associated with preeclampsia, particularly early onset disease.

Introduction

Women at risk of preeclampsia are monitored closely in pregnancy, and started on preventative interventions such as aspirin to reduce adverse outcomes. Early commencement of these interventions has the potential for maximal benefit [1]. Our current assessment in early pregnancy for preeclampsia is mainly based on maternal history [2]. However, such a risk factor approach has limited predictive accuracy [3,4]. There is a need for an accurate first trimester screening test for preeclampsia. Studies on prediction models based on clinical characteristics have highlighted the need for additional tests such as biomarkers to improve performance [5].

Angiogenic biomarkers, considered to be the markers of placental function, have the potential to identify early in pregnancy, the subsequent risk of preeclampsia. Abnormal angiogenic biomarkers are observed when impaired placental perfusion leads to placental ischemia, with release of inflammatory factors that contribute to the clinical symptoms of the disease [6–10]. Although, primary studies have evaluated the role of various biomarkers in early pregnancy, the overall strength of association between abnormal biomarkers in early pregnancy and preeclampsia is not clear. Furthermore, the relationship between maternal blood biomarkers and the timing of preeclampsia onset needs to be evaluated.

We undertook a systematic review and meta-analysis to evaluate the magnitude of association between abnormal maternal

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blood biomarkers in the first trimester and subsequent development of preeclampsia.

Materials and methods

We undertook the systematic review with a prospective protocol in line with current recommendations [11]. We searched Cochrane, Embase and Medline databases from database inception up to April 2013 to identify relevant citations. We used the following combination of search terms and their word variants: first trimester AND biomarkers (PlGF, betaHCG, AFP, PAPP-A, nitric oxide, SVEGFR-1, sFlt-1, inhibin-a, unconjugated oestriol, endoglin, activin-a, PP13, ADAM-12, dimethylarginine, pentraxin-3, *p*-selectin, adrenomedullin, visfatin, cell free DNA, cell free fetal DNA) AND preeclampsia. We examined the reference lists of all known primary and review articles to capture articles missed by the electronic searches. Language restrictions were not applied. We contacted the authors of primary studies if relevant data were not reported.

Study selection was performed in two stages. First, the electronic searches were scrutinized and appropriate studies were identified. Second, two independent reviewers (RA and KC) reviewed the full text of the identified papers and selected the studies that fulfilled the inclusion criteria. Any disagreements were resolved with input from the third reviewer (ST). We included those studies that evaluated the association between biomarkers in the first trimester and any preeclampsia. We accepted the following definition for preeclampsia: persistently high systolic ($\geq$140 mmHg) or diastolic ($\geq$90 mmHg) blood pressure and proteinuria ($>$0.3 g/24 h or a dipstick result of $>$1+, equivalent to 30 mg/dl in a single urine sample or spot urine protein/creatinine ratio $>$30 mg protein/mmol creatinine) of new onset after 20 weeks of gestation. To be included, studies should describe the occurrence of preeclampsia conditional on the test and provide the result as means and standard deviations for continuous outcomes or in such a way that 2 $\times$ 2 classification tables could be constructed for dichotomous outcomes.

Where there were multiple publications of one dataset we only included the most recent or most complete paper. Data extraction was done by two independent researchers (RA and KC).

The quality of the study methodology was assessed using the Newcastle-Ottawa scale [12]. For case control studies, we assessed the risk of bias in: the definition, selection and representativeness of the cases and controls; the comparability of the groups; and the ascertainment and completeness of exposure. For the cohort studies, we evaluated the risk of bias in: the selection and representativeness of the cohorts; their comparability; the exposure and outcome assessment; and the completeness of follow up. Studies were considered to have a low risk of bias if they scored 4 stars for selection, 2 for comparability or 3 stars for exposure or outcome. Studies that scored 0 or 1 star for selection, 0 stars for comparability or 0 or 1 star for exposure or outcome were considered to have high risk of bias. Studies scoring between these were regarded to have medium risk of bias.

We summarized the results as odds ratios with 95% confidence intervals. When the marker concentration was provided as a continuous variable, we expressed the results as standardized mean differences with standard deviation. We pooled the results using an inverse variance weighted random effect approach. Both continuous and dichotomous data were meta-analyzed by converting odds ratios to effect size. This method enabled us to summarize the results without loss of data and prevented data from being misleading [13]. Egger's test was used to explore for publication bias. All analyses were performed with Revman 5.0 and Stata 12.1 statistical software.

Results

Characteristics of the included studies

From 1071 relevant citations, we identified 88 studies for further assessment. After full evaluation of these, we included 30 studies in the review (Fig. 1, Appendix 1) [7,14–42]. Seventeen (17/30, 57%) were case control studies and 13 (13/30, 43%) were cohort studies. Sample sizes ranged from 45 to 47,922. Half of the studies (15/30, 50%) specified inclusion and exclusion criteria in detail. Ten studies were on low risk women and eight included high risk women. The high risk studies included women with previous preeclampsia, pre-existing hypertension, diabetes or renal disease. Risk status was not reported in 12 studies. Women with multiple pregnancies and fetal anomalies were excluded in all studies that reported in detail.

The markers evaluated in these studies were PAPP-A (12 studies), PlGF (8 studies), PP13(5 studies), beta HCG (4 studies), soluble endoglin (5 studies), inhibin-A (5 studies), sFlt-1 (7 studies), *p*-selectin (1 study), pentraxin (1 study) and VEGF (1 study). All markers were evaluated in the first trimester of pregnancy for early, late or any onset preeclampsia.

Quality of the included studies

Two thirds of the cohort studies (8/13, 62%) had a medium risk of selection bias, two thirds had high risk of comparability bias (8/13, 62%) and 90% (12/13) were low risk for outcome assessment. Amongst case control studies, 12%, (2/17) had a high risk of selection bias, 59% (10/17) were medium risk for comparability and almost half (41%) were low risk for outcome assessment (7/17). The quality assessment is provided in Fig. 2, and in Appendix 2.

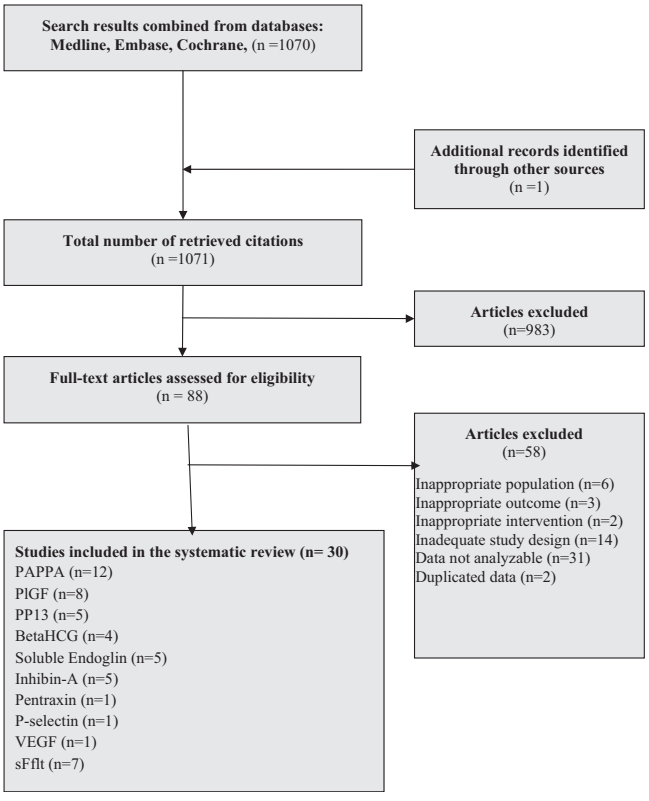

Fig. 1. Flow chart of study identification and study selection in the systematic review of biochemical markers and their prediction of preeclampsia.