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The predictive role of serum copeptin levels in preeclampsia: a meta-analysis

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ABSTRACT

Preeclampsia represents a major pregnancy complication associated with high fetal and maternal morbidity rates. Early prediction of the disease is essential to effectively discriminate the population of pregnant women that would benefit the most from preventive measures, especially aspirin administration. Nonetheless, the best screening model to be widely used in clinical practice remains under investigation. The present systematic review aims to accumulate current literature evidence in order to compare copeptin concentration among normotensive and preeclamptic women and find out whether its serum level alteration precedes the onset of the disease. All observational studies will be held eligible. Medline, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science databases will be searched form inception. The main outcome of interest will be the comparison of copeptin levels between the preeclamptic and the normotensive groups of pregnant women. A random-effects statistical model will be used to provide pooled estimates of standardized mean differences and 95% confidence intervals. Subgroup analysis will be performed on the basis of trimester at sampling (1st, 2nd or 3rd), preeclampsia severity (mild or severe) and onset (early or late).

1 Review title: The predictive role of serum copeptin levels in preeclampsia: a meta-analysis

2 Review question: The present systematic review aims to compare copeptin concentration among normotensive and preeclamptic women and assess whether its serum level alteration precedes the onset of the disease. Population: Pregnant women in any gestational trimester Exposure: Preeclampsia Comparison: Healthy pregnant women Outcome: Serum copeptin levels Study type: Observational studies (prospective/retrospective cohort, cross-sectional, case-control, nested case-control)

3 Literature search: Literature search will be conducted using the Medline, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science databases. Google Scholar database and the reference lists of the included studies (“snowball” method) will be also screened to identify additional articles. Databases will be searched from inception by using the following key-terms: “copeptin, vasopressin, provasopressin, avp, pro-avp, proavp, ct-proavp, cpp, antidiuretic hormone, adh, preeclampsia, pre-eclampsia”.

4 Condition or domain being studied: The present meta-analysis will evaluate serum copeptin levels among preeclamptic and healthy pregnant women. Preeclampsia represents a major pregnancy complication associated with high fetal and maternal morbidity rates. Its pathophysiology is complex; it is hypothesized that deficient trophoblast invasion in conjunction with the release of various angiogenic and oxidative mediators into maternal circulation leads to endothelial dysfunction, increased vascular reactivity and activation of the coagulation cascade. Early prediction of the disease is essential to effectively discriminate the population of pregnant women that would benefit the most from preventive measures, especially aspirin administration. Nonetheless, the best screening model to be widely used in clinical practice remains under investigation.

5 Participants/population: Preeclampsia will be detected as new-onset hypertension (Systolic blood pressure >140 mmHg and/or Diastolic blood pressure >90 mmHg) after the 20th gestational week combined with either the presence of proteinuria or maternal end-organ dysfunction. Early-onset preeclampsia will be diagnosed as preeclampsia before the 34th week of pregnancy. Severe preeclampsia will be defined as severe hypertension (Systolic blood pressure >160 mmHg and/or Diastolic blood pressure >110 mmHg) or presence of maternal organ dysfunction. Exclusion criteria: chronic hypertension, gestational hypertension, eclampsia, hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome or other pregnancy-related complications.

6 Intervention(s), exposure(s): Evaluation of serum copeptin levels among preeclamptic and healthy normotensive pregnant women. No trimester or laboratory restrictions will be applied.

7 Comparator(s)/control: Normotensive women without proteinuria, edema, signs of maternal organ dysfunction or any pregnancy-related complications.

8 Types of study to be included: Observational studies (prospective & retrospective cohorts, case-control, cross-sectional, nested case-control) will be included. Case reports, review articles, posters, letters to the editor, animal and in vitro studies will be excluded.

9 Main outcome(s): Comparison of serum copeptin levels among preeclamptic and healthy pregnant women.

10 Data extraction: The process of study selection will be performed in 3 consecutive stages. Firstly, titles and abstracts of all electronic papers will be screened to assess their potential eligibility. All articles presumed to meet the criteria will be retrieved as full-texts. Subsequently, all observational studies reporting the outcomes of interest will be selected. Data extraction will be made by two authors independently. Any potential discrepancies concerning retrieval of articles will be resolved through the consensus of all authors. The extracted data will include the following parameters: year of publication, country, sample size, study design, eligibility criteria, preeclampsia definition, laboratory assay for copeptin measurement, type of sample (serum or plasma) and timing of measurement.

11 Risk of bias (quality) assessment: The Newcastle-Ottawa Scale (NOS) score will be used to evaluate the methodological quality of all included studies. The risk of bias in case-control studies will be assessed by taking into consideration the following domains: selection of cases and controls, comparability of the patient groups, ascertainment of exposure and non-response rate. Comparability will be assessed by taking into account whether studies controlled for maternal and gestational age. Cohort studies will be evaluated on the grounds of patient selection process, comparability of the exposed and non-exposed cohorts, assessment of outcome and adequacy of the follow-up period.

12 Strategy for data synthesis: A random-effects (DerSimonian-Laird) model will be used to provide pooled estimates of standardized mean difference and 95% confidence intervals. Diagnostic accuracy meta-analysis will be performed if >4 studies had introduced cut-off values and reported enough data for the construction of 2x2 tables. Inter-study heterogeneity will be evaluated by the between-study variance ($\tau 2$) and the inconsistency index (I2), with I2 >50% indicating high heterogeneity. The impact of heterogeneity on clinical outcomes will be quantified by calculating the 95% prediction intervals, which indicate the effects to be expected in future populations. Significant heterogeneity will be detected when the exact opposite effect of the pooled estimate will be included in the 95% prediction intervals. In addition, based on the estimated prediction intervals, the probability that a new study will demonstrate a null or negative effect (SMD ≤ 0) will be also calculated.

13 Analysis of subgroups or subsets: Subgroup analysis will be conducted on the basis of trimester at sampling (1st, 2nd or 3rd), preeclampsia severity (mild or severe) and onset (early or late).

14 Sensitivity analysis: The credibility ceiling test will be used under the assumption that each observational study is only able to provide limited certainty that an effect is in a particular direction. In this context, a new wider variation will be calculated for each study by applying credibility ceilings of 5%. Moreover, sensitivity analyses will be performed by separately examining prospective cohort studies, studies with large sample size (defined as ≥ 80 women), studies using serum samples and enzyme-linked immunosorbent assays (ELISA) for copeptin measurement, as well as those at low risk of bias (defined as NOS score ≥ 8).

15 Keywords: copeptin; vasopressin; preeclampsia; prediction; meta-analysis