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The hypothalamic-neuro-hypophyseal axis in preeclampsia: a systematic review with a subgroup meta-analysis of copeptin levels worldwide

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Abstract

High concentrations of copeptin, a marker of arginine vasopressin secretion, precede the clinical features of preeclampsia, a life-threatening maternal condition. This study aims to investigate the influence of demographic variations on copeptin concentrations and the overall effect of the hypothalamic-neuro-hypophyseal axis on preeclampsia. We also aim to employ this data to train a machine learning clustering technique, as well as to evaluate the occurrence of Single Nucleotide Polymorphisms (SNPs) associated with arginine vasopressin hypersecretion and metabolism. The comparison of copeptin levels between the preeclamptic and normotensive groups of pregnant women will be the primary outcome of interest. 95% CIs and pooled estimates of standardised mean differences will be provided using a random-effects statistical model.

Troubleshooting

Abstract

1 High concentrations of copeptin, a marker of arginine vasopressin secretion, precede the clinical features of preeclampsia, a life-threatening maternal condition. This study aims to investigate the influence of demographic variations on copeptin concentrations and the overall effect of the hypothalamic-neuro-hypophyseal axis on preeclampsia. We also aim to employ this data to train a machine learning clustering technique, as well as to evaluate the occurrence of Single Nucleotide Polymorphisms (SNPs) associated with arginine vasopressin hypersecretion and metabolism. The comparison of copeptin levels between the preeclamptic and normotensive groups of pregnant women will be the primary outcome of interest. 95% CIs and pooled estimates of standardised mean differences will be provided using a random-effects statistical model.

Untitled section

2 1 Review title: The hypothalamic-neuro-hypophyseal axis in preeclampsia: a systematic review with a subgroup meta-analysis of copeptin levels worldwide

2 Review question: The current systematic review is an actualisation of the relationship between the hypothalamic-neuro-hypophyseal axis and preeclampsia via a meta-analysis, but focussing on exploring how the demographic area effects the elevation of the blood copeptin concentration in PE. Population: Pregnant women in any gestational trimester Exposure: Preeclampsia Comparison: Healthy pregnant women Outcome: Copeptin levels Study type: Observational studies (prospective/retrospective cohort, cross-sectional, case-control, nested case-control)

3 Literature search: For the meta-analysis nineteen studies were obtained from five databases (Google Scholar, Embase, Scopus, PubMed, and Semantic Scholar) using the following key terms: "preeclampsia-AND-vasopressin-OR-copeptin-OR-oxytocin". Other three registries were also screened to identify additional information related to polymorphisms involving the hypothalamic-neuro-hypophyseal axis in preeclampsia

4 Condition or domain being studied: The subgroup meta-analysis compared serum copeptin levels in preeclamptic and healthy pregnancies worldwide to see if this hypothalamic-neuro-hypophyseal axis imbalance is present worldwide

5 Participants/population: Preeclampsia was defined as an increase in systolic blood pressure > 140 mmHg after the 20th week of gestation with the presence of proteinuria and/or maternal organ dysfunction. Early-onset and late onset preeclampsia were defined as occurring before or after the 34th week of gestation

respectively. Exclusion criteria include persistent hypertension, gestational hypertension, and other pregnancy-related problems

6 Intervention(s), exposure(s): Preeclamptic pregnant women, with no trimester of sampling restrictions

7 Comparator(s)/control: Normotensive pregnant women without proteinuria or other pregnancy-related complications

8 Types of study to be included: Observational studies (prospective & retrospective cohorts, case-control, cross-sectional, nested case-control)

9 Main outcome(s): To explore the impact of demographic variations on copeptin concentrations and the overall effect of the hypothalamic-neuro-hypophyseal axis on PE. Comparing preeclamptic and healthy pregnant women from different continents

10 Data extraction: The full versions of the observational studies documenting copeptin concentrations across all three trimesters will be retrieved after removing duplicates and reviewing the titles and abstracts of all the publications considered likely to meet the eligibility criteria using the Rayyan software. After defining the search terms and databases, the studies will be selected through a peer review method. Confusions regarding retrieval will be resolved by consensus between the researchers. The extracted data will include: author, year, country, study design, gestational trimester, and number of records in each group. In addition, studies evaluating genomic variants known to influence the development of preeclampsia in genes related to arginine vasopressin signalling/metabolism were accepted, since we intend to summarise these SNP frequencies by noting in a table how geographic location influences CPP concentration in PE cases.

11 Risk of bias (quality) assessment: The methodological quality of the evidence of all the included studies will be evaluated using the Newcastle-Ottawa Scale (NOS) score and verified by the Grading of Recommendations Assessment Development and Evaluation (GRADE) framework. For the risk of bias, case-control studies will be assessed taking into account factors such as the selection of cases, the comparability of groups and the determination of exposure. While cohort studies will be assessed based on the selection process, the comparability of exposed and unexposed cohorts and the evaluation of results.

12 Data synthesis: Cochrane's Review Manager wil be used to run a random-effects association meta-analysis with pooled estimates of the standardised mean difference (SMD) and confidence intervals (CI) to determine the combined mean effect based on the inverse variance. It will includ cohort, cross-sectional and case-control studies where the plasma was collected to assess the CPP concentration through Enzyme-

Linked Immunosorbent Assay (ELISA) or Luminescent Immunoassay (LIA). We intend to use the DerSimonian and Laird methods to build forest plots and verify Studies' heterogeneity (tau2) and the Inconsistency Index (I2)

13 Subgroup analysis: A subgroup meta-analysis will be performed by dividing the data by continent/region to examine whether the region of sampling influences the elevation in CPP concentration in PE worldwide to elucidate this geographic link

14 Sensitivity analysis: We aim to do the sensitivity analysis carring out by removing the extrapolated values obtained from the funnel plot after observing substantial heterogeneity and asymmetry in the funnel plot

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