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The role of serum adipokine levels in preeclampsia: a systematic review

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Abstract

Preeclampsia represents a serious pregnancy complication with high fetal and maternal morbidity and mortality rates.Accurate prediction of the disease is essential to effectively discriminate the population of pregnant women to provide preventive measures, especially aspirin administration. Adipokines have been hypothesized to be involved in preeclampsia pathophysiology, due to their actions in regulating placental angiogenesis. Several observational studies have evaluated serum adipokine levels among preeclamptic women, although no consensus currently exists concerning their exact role in the disease. Therefore, a systematic review is planned aiming to accumulate all the available evidence in the field and assess whether serum adipokines can serve as useful predictive tools in preeclampsia.

Troubleshooting

1 Review question The present systematic review aims to investigate whether adipokine levels differ among preeclamptic and healthy pregnant women. Population: Pregnant women in any gestational trimester Exposure: Preeclampsia Comparison: Healthy pregnant women Outcome: Adipokine serum levels Study type: Observational studies (prospective/retrospective cohort, cross-sectional, case-control, nested case-control)

2 Searches MEDLINE, Scopus, CENTRAL, ClinicalTrials.gov and Google Scholar will be systematically searched from inception. The full reference list of the included studies will be also searched (snowball method). No date/language restrictions will be applied. The main search terms will include: "adipokine, leptin, adiponectin, resistin, visfatin, vaspin, omentin, chemerin, ghrelin, irisin, nesfatin, progranulin, retinol binding protein, rbp4, rbp-4, fatty acid binding, fabp4, fabp-4, fibroblast growth factor, fgf21, fgf-21, preeclampsia, pre-eclampsia".

3 Condition or domain being studied The present systematic review will evaluate the potential association of serum adipokines with the development of preeclampsia. Preeclampsia represents a serious pregnancy complication with high fetal and maternal morbidity and mortality rates. Its pathogenesis is complex; it is assumed that poor 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. Accurate prediction of the disease is essential to effectively discriminate the population of pregnant women to provide preventive measures, especially aspirin administration. Nevertheless, the optimal screening model remains under investigation.

4 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 when occuring 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. Exlcusion criteria: gestational hypertension, no adipokine measurement, no control group of healrhy pregnant women

5 Intervention(s), exposure(s) Evaluation of serum levels of adipokines (leptin, adiponectin, visfatin, resistin, vaspin, omentin, irisin, ghrlin, nesfatin, chemerin, progranulin, retinol binding protein-4, fatty acid binding protein-4, fibroblast growth factor-21) among preeclamptic and healthy pregnant women. No trimester or laboratory assay restrictions will be applied.

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

7 Types of study to be included Observational studies (prospective & retrospective cohorts, case-control, cross-sectional, nested case-control) will be included. Case-reports, small case series (<10 patients), letters to the editor, conference proceedings, animal studies and review articles will be excluded.

8 Main outcome(s) Comparison of serum adipokine levels among preeclamptic and healthy pregnant women.

9 Additional outcome(s) Subgroup analysis will be performed on the basis of: pregnancy trimester at sampling, preeclampsia severity, preeclampsia onset, obesity.

10 Data extraction The process of study selection will be performed in 3 copnsecutive 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 possible discrepancies concerning retrieval of articles will be resolved through the consensus of all authors. The extracted data will include the following parameters: name of first author, year of publication, exclusion criteria, study design, country, trimester of measurement, laboratory assay method, fasting state, maternal age, gestational age at sampling, body mass index and systolic blood pressure, as well as the outcomes of interest (serum adipokine levels).

11 Risk of bias (quality) assessment The quality of the included studies will be evaluated using the Newcastle-Ottawa Scale (NOS) score. Case-control studies will be assessed regarding the risk of bias on the domains of patient selection, comparability of cases and controls, ascertainment of exposure and non-response rate. The risk of bias in cohort studies will be assessed on the basis of selection and comparability of the exposed and non-exposed cohorts, as well as the assessment of outcome and the adequacy of the follow-up period. The NOS score will be evaluated by two authors independently; any disagreements will be resolved through their consensus. Credibility of evidence will be evaluated under the GRADE framework (GRADE-CERQual tool) by judging outcomes on the grounds of methodological limitations, coherence, adequacy of data and relevance.

12 Strategy for data synthesis A qualitative synthesis is planned to performed as the expected inter-study heterogeneity is high due to differentiations of laboratory assays across different settings. Moreover, adipokine serum levels often present skewed distributions; thus, precluding quantitative meta-analysis. The results will be summarized by tabulating the number of studies in which the examined adipokines are increased, decreased or unchanged in preeclamptic pregnancies. Furthermore, the quality of evidence regarding serum levels of various adipokines in preeclampsia will be presented.

13 Analysis of subgroups or subsets Subgroup analysis will be performed based on preeclampsia severity (mild vs. severe) and onset (early vs. late), as well as trimester of

measurement (1st, 2nd and 3rd) and presence of obesity.

14 Keywords adipokine preeclampsia leptin adiponectin resistin systematic review