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# BMJ Open

## Metabolomics for prediction of hypertension in pregnancy: a systematic review and meta-analysis protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040652
Article Type:	Protocol
Date Submitted by the Author:	19-May-2020
Complete List of Authors:	Mayrink, Jussara; Universidade Estadual de Campinas Faculdade de Ciencias Medicas Leite, Debora; Campinas' State University, Department of Tocogynecology; Universidade Federal de Pernambuco, Costa, Maria Laura Cecatti, Jose; University of Campinas, Obstetrics and Gynecology
Keywords:	Hypertension < CARDIOLOGY, Prenatal diagnosis < OBSTETRICS, EPIDEMIOLOGY

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## 1 SYSTEMATIC REVIEW PROTOCOL

2 **Metabolomics for prediction of hypertension in pregnancy: a systematic**  
3 **review and meta-analysis protocol**4  
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## 25 Abstract

26 **Introduction:** hypertension is a very important cause of maternal morbidity and mortality  
27 worldwide, despite efforts on prevention. The lack of a tool to provide effective and early  
28 prediction of hypertension for a high-risk group may contribute to improve maternal and  
29 fetal outcomes. Metabolomics has figured out as a promised technology to contribute to  
30 the improvement on hypertension in pregnancy prediction. **Methods and analysis:** our  
31 primary outcome is hypertensive disorders of pregnancy. A detailed systematic literature  
32 search will be performed in electronic databases, using controlled terms 'preeclampsia',  
33 'hypertensive disorders', 'metabolomics' and 'prediction' (and their variations). Studies  
34 from the latest twenty years will be included, except case reports, reviews, cross-sectional  
35 studies, letter to editors, expert opinions, commentaries papers or non-human research. If  
36 possible, we will perform a meta-analysis. Two peer reviewers will independently perform  
37 the search and in cases of discordance a third reviewer will be consulted. **Ethics and**  
38 **dissemination:** the results of this review will present the current use and performance of  
39 metabolomics for predicting gestational hypertension. Such data could potentially guide  
40 future studies and interventions to improve existing prediction models.

## 41 Strengths and limitations of this study

- 42 • Electronic search will cover the most important current available scientific  
43 databases for health research;
- 44 • There will not be a language restriction;
- 45 • Considering the complexity of Metabolomics technology and its methods, there  
46 would be a limitation to perform a quantitative synthesis.

## 47 Key words

48 Preeclampsia, pregnancy, hypertension, hypertensive disorders, hypertensive syndromes,  
49 metabolomics, metabolome

50 **Prospero register number: CRD42018097409**

## 51 Introduction

52 Hypertensive disorders in pregnancy consist of a group of conditions including  
53 preeclampsia, gestational hypertension, preeclampsia superimposed to chronic  
54 hypertension, white coat hypertension, masked hypertension and transient hypertension <sup>1</sup>  
55 <sup>2</sup>and appear as the second cause of maternal death in the world according to a study  
56 performed by the World Health Organization between 2003 and 2009 <sup>3</sup>. Preeclampsia is the  
57 leading cause of maternal morbidity and mortality in Brazil and in several other low-and  
58 middle-income countries <sup>4,5</sup>. Its prevalence can vary according to the set of analyses, but  
59 the number ranges from 2 to 10% of all pregnancies <sup>4</sup>. Every year, around 80 thousand  
60 women die because of preeclampsia and its complications <sup>6</sup>, despite potential prevention  
61 implemented by low-dose aspirin <sup>7</sup>. This intervention can represent a reduction rate of  
62 around 50% in the incidence of the early-onset preeclampsia cases, which developed  
63 preeclampsia before 34 weeks of gestation <sup>7,8</sup>. In this scenario, prediction of pregnant  
64 women under high-risk to develop preeclampsia is a key topic.

65 Some biomarkers have been proposed as earlier predictors (placental growth factor  
66 - PIGF, pregnancy-associated plasma protein A-PAPP-A) combined with clinical factors  
67 (pulsatility index of uterine arteries at Dopplervelocimetry exam, mean arterial blood  
68 pressure), showing different and sometimes conflicting detection rates <sup>9-12</sup>. These studies  
69 present limitations regarding the number of participants enrolled and heterogeneity to  
70 assess the prediction performance of those factors. Furthermore, the proposed prediction  
71 models from combining those factors outline better detection rates for early-onset  
72 preeclampsia cases compared to late-onset cases <sup>13-15</sup>.

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2  
3 73 In the last decade, with the broad application of omics technologies, metabolomics  
4  
5 74 has been pointed as a promising tool for the identification of early predictors for many  
6  
7  
8 75 health disturbances <sup>16-18</sup> and preeclampsia is one of them. Through metabolomics, it would  
9  
10 76 be possible to identify metabolites involved in the final line of gene expression and a  
11  
12 77 phenotypic signature in high resolution of the disease to be studied <sup>19-21</sup>. Studies have  
13  
14 78 provided some insights about preeclampsia prediction through metabolites, belonging to  
15  
16 79 different chemical classes and showing different performances <sup>20-23</sup>. In 2010, Kenny et al  
17  
18 80 provided the initial knowledge on the topic, identifying 14 metabolites belonging to  
19  
20 81 different chemical classes. When combined in an algorithm they showed a very good  
21  
22 82 performance, with an Area under the Curve (AUC) of 0.94 in a discovery phase of the study  
23  
24 83 and a detection rate of 77%, considering a false-positive rate of 10% <sup>22</sup>. It represents a very  
25  
26 84 important tool option for prediction, especially with regard to cases of late-onset  
27  
28 85 preeclampsia, which are the majority and the most difficult cases to predict <sup>13-15</sup>. Thus, in  
29  
30 86 the sense of the inexistence of a systematic review protocol registered in this topic as well  
31  
32 87 as a systematic review in progress or published, the main objective of this systematic review  
33  
34 88 is to determine the accuracy of metabolomics for predicting hypertensive disorders of  
35  
36 89 pregnancy.  
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### 91 **Question formulation**

92 In view of the social and economic implication of hypertensive disorders, their  
93 consequences to maternal and fetal lives worldwide and the lack of a useful screening test,  
94 in parallel to the increase of applicability of omics technologies, this systematic review will

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2  
3 95 be guided by this question: what is the performance of metabolomics for predicting  
4  
5 96 gestational hypertensive disorders? It is in accordance with the PICO method <sup>24</sup> and  
6  
7  
8 97 associated with the search strategy provided a preliminary flow chart of studies as  
9  
10  
11 98 summarized in figure 1.  
12

13 99

## 100 **Methods and Analysis**

### 101 ***Search Strategy***

102 Electronic searches of literature will be carried out with these following databases: PubMed,  
103 EMBASE, Scopus, Web of Science, Latin America and Caribbean Health Sciences Literature  
104 (LILACS), Scientific Electronic Library Online (SciELO), Health Technology Assessment (HTA),  
105 Database of Abstracts of Reviews of Effects (DARE). We will include studies from the latest  
106 twenty years, considering that the vast majority of manuscripts on metabolomics are from  
107 this century. Our search strategy will combine terms with Boolean connectors related to  
108 the following categories: 1) hypertensive disorders, preeclampsia, pregnancy; 2)  
109 metabolomics, metabolome; and 3) screening, prediction. The Boolean connectors will be  
110 adapted according to the database used. We decided to use regular terms – not MESH or  
111 Emtree terms – taking into account the number of databases consulted, in order to use  
112 always the same terms for all of them. In addition, we will search reference list of included  
113 articles, doing the backtracking of references. There will not be a language restriction.  
114 Before final publication, we will perform a new search in the databases in order to check if  
115 any study was published during the period of the systematic review elaboration. The  
116 databases exploration process and its results will follow the PRISMA Statement <sup>25</sup>.



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3 117 ***Study selection process***  
4

5 118 After searching all sources of databases cited above, all the citations will be exported into  
6  
7  
8 119 EndNote® software. Firstly, two reviewers (JM and DFBL) will independently assess titles  
9  
10 120 and abstracts. Only papers considered potentially relevant according to the inclusion  
11  
12 121 criteria will be retrieved for further consideration. Cases of divergence will be analyzed by  
13  
14 122 a third reviewer (MLC) who will do the final decision. A fourth reviewer (JGC) will check all  
15  
16 123 procedures before approving the data extraction.  
17

18  
19  
20 124 ***Study inclusion criteria***  
21

22 125 Hypertensive disorders developed at any gestational age will be considered the domain  
23  
24 126 studied. Previous other chronic conditions (diabetes, renal diseases, etc.) will be reported  
25  
26 127 for stratification of analysis if the data allow for this. Original studies – including diagnostic  
27  
28 128 studies - involving pregnant women are the inclusion criteria, and congenital malformation  
29  
30 129 is the exclusion criteria.  
31  
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34  
35 130 ***Interventions/exposure***  
36

37 131 Prediction of hypertensive disorders through metabolomics technologies is the intervention  
38  
39 132 to be studied. The biomarker analysis should have been performed on samples taken before  
40  
41 133 the hypertensive disorder diagnosis.  
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45 134 ***Design***  
46

47 135 Our systematic review will include original studies (cohort or case control studies), including  
48  
49 136 single or multiple pregnancies, as the studied population, and hypertensive disorders  
50  
51 137 developed at any time of pregnancy, as the outcome of interest. We will exclude any studies  
52  
53 138 that are: cross-sectional studies, case reports, editorials, letter to editors, commentaries,  
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139 expert opinions, any type of reviews, and experimental studies with animals, and when it is  
140 not possible to extract the data about the outcomes of interest.

### 141 **Outcomes**

142 We will include studies reporting outcomes of any hypertensive disorder developed during  
143 pregnancy. Our primary outcome is preeclampsia, defined as the onset of hypertension (a  
144 systolic blood pressure of 140 mmHg or more and/or a diastolic blood pressure of 90 mmHg  
145 or more) after 20 weeks of gestation, measured at least in two different occasions,  
146 combined with: (1) proteinuria (300 mg/day or at least 1g/L [1+] on dipstick testing or spot  
147 urine protein/creatinine >30mg/mmol [0.3mg/mg]) or (2) systemic complications or (3)  
148 uteroplacental dysfunction (fetal growth restriction)<sup>1</sup>. By systemic complications, we will  
149 consider:

- 150 ✓ Hematological complications (thrombocytopenia- platelet count below 150,000/dL,  
151 disseminated intravascular coagulation, hemolysis);
- 152 ✓ Hepatic dysfunction (elevated transaminases – at least twice upper limit of normal +-  
153 right upper quadrant or epigastric abdominal pain);
- 154 ✓ Neurological dysfunction (examples include eclampsia, altered mental status, blindness,  
155 stroke or more commonly hyperreflexia when accompanied by clonus, severe  
156 headaches when accompanied by hyperreflexia, persistent visual scotomata;
- 157 ✓ Renal dysfunction (creatinine > 1.2mg/dL);

158 Secondary outcomes include:

- 159 ✓ Early-onset preeclampsia: when occurs before or at 33 weeks of gestation<sup>26</sup>;
- 160 ✓ Late-onset preeclampsia: when occurs at or after 34 weeks of gestation<sup>26</sup>.

- 1  
2  
3 161 ✓ Gestational hypertension: de novo development of high blood pressure after 20 weeks  
4  
5 162 of gestation (a systolic blood pressure of 140 mmHg or more and/or a diastolic blood  
6  
7 163 pressure of 90 mmHg or more), without any of the abnormalities that define  
8  
9 164 preeclampsia as discussed above <sup>1</sup>  
10  
11  
12  
13 165 ✓ White coat hypertension: it is demonstrated when a normal blood pressure is registered  
14  
15 166 during 24 hours ambulatory monitoring in the first half of pregnancy <sup>1</sup>  
16  
17  
18 167 ✓ Preeclampsia superimposed on chronic hypertension: in a patient with high blood  
19  
20 168 pressure predating the pregnancy, it is registered the occurrence of preeclampsia <sup>1</sup>  
21  
22  
23 169 ✓ Masked hypertension: is characterized by blood pressure that is normal at office or clinic  
24  
25 170 but elevated at other times, most typically diagnosed by 24 hours ambulatory blood  
26  
27 171 pressure monitoring <sup>2</sup>  
28  
29  
30 172 ✓ Transient gestational hypertension: is hypertension that arises in the second or third  
31  
32 173 trimester. The hypertension is detected in the clinic but then settles with repeated  
33  
34 174 blood pressure readings <sup>2</sup>  
35  
36  
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40 176 **Data extraction**

41  
42 177 Data will be extracted through a standardized data compilation form in duplicate to avoid  
43  
44 178 errors. The variables of interest from each included study are: authors, country, year of  
45  
46 179 publication, study design, number of participants, preeclampsia prevalence, gestational age  
47  
48 180 of recruitment, biological samples utilized, laboratory methods, metabolomics technology  
49  
50 181 applied and metabolites. The metabolites will be matched with the Human Metabolome  
51  
52 182 Database (HMDB) in order to check their biological function and chemical subclass. Missing  
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183 data will be requested from study authors. Pairs of data-extraction forms will be checked  
184 for discrepancies.

### 185 ***Quality Appraisal***

186 The same two reviewers (JM and DFBL) who judged eligibility of papers will independently  
187 assess the risk of bias in included studies, but this time rating the methodological quality of  
188 the primary research. A third reviewer (MLC) will solve divergences when needed. Quality  
189 Assessment of Diagnostic Accuracy Studies (QUADAS-2) is the standard scale to be applied  
190 to assess internal validity<sup>27</sup>. This tool is composed by four domains: patient selection, index  
191 test (metabolomics technique), reference standard (arterial blood pressure) and flow and  
192 timing of patient inclusion and follow up. Each domain is assessed in terms of risk of bias  
193 and the first three are assessed in terms of concerns regarding applicability. For each  
194 domain, every study will be labelled as “low”, “high” or “unclear” risk of bias.

195 Funnel plots and sensitivity and cumulative analyses will be applied for detection of  
196 temporal trends and publication bias.

### 197 ***Strategy for data synthesis***

198 In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis  
199 (PRISMA), a flow diagram will be drawn<sup>25</sup>. Tables will show data regarding studies  
200 characteristics and risk of bias assessment for included and excluded studies. Narrative data  
201 will be analyzed and structured according to the outcomes: preeclampsia, gestational  
202 hypertension, transient gestational hypertension, white coat hypertension, masked  
203 hypertension. If possible, we are going to perform a subgroup analysis according to the  
204 metabolomics methods applied: gas or liquid chromatography, coupled with mass

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3 205 spectrometry, or proton nuclear magnetic resonance. We also intend to perform a  
4  
5 206 sensitivity analysis on the basis of early and late preeclampsia cases if sufficient studies will  
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8 207 be found.  
9

10 208 A meta-analysis will be performed (hierarchical summary receiver characteristic operating  
11  
12 209 curve, HSROC) and accuracy measures will be calculated depending on data availability.  
13  
14  
15 210 Heterogeneity will also be assessed, through I-square test, Hotelling's T-squared test and  
16  
17  
18 211 Cochran's Q test.  
19

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### 23 213 ***Ethics and dissemination***

24  
25 214 Prediction of hypertensive disorders has been studied over the years with specific  
26  
27 215 challenges. Among nulliparous for example, there is no history of previous events and a  
28  
29  
30 216 previous history of preeclampsia, is considered the most consistent predictive risk factor <sup>28</sup>.  
31  
32 217 Another challenge to overcome is regarding to late-onset preeclampsia cases, which  
33  
34  
35 218 represent the majority of them. As cited above, the algorithms composed by biochemical  
36  
37 219 and clinical factors showed better results with early onset cases of preeclampsia <sup>13-14</sup>.  
38

39  
40 220 Metabolomics is a very complex technology and it has emerged as a possibility for  
41  
42 221 prediction of adverse pregnancy outcomes <sup>29-31</sup>. The techniques employed are nuclear  
43  
44 222 magnetic resonance spectroscopy, gas or liquid chromatography-mass spectrometry,  
45  
46  
47 223 Fourier transform infrared spectrometry and capillary electrophoresis <sup>31</sup>. Because of this  
48  
49 224 complexity, results may be different concerning to the metabolites found. Consequently,  
50  
51  
52 225 generalizing results is also a challenge to overcome. This systematic review will contribute  
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226 to optimize the knowledge about the metabolites found in the studies and perhaps classify  
227 them according to HMDB, enabling quality translational research.

228 In addition, this systematic review will contribute to establish the current state of  
229 knowledge concerning the capacity of metabolomics to predict the occurrence of  
230 preeclampsia. Taking into account that this outcome involves relevant consequences for  
231 maternal and neonatal lives, the development of a tool that would predict preeclampsia is  
232 essential. Furthermore, the results of this systematic review could be used to guide future  
233 studies in this field. Once published, this systematic review will be free available in an open  
234 access scientific journal.

### 235 ***Patient and Public Involvement***

236 Patients or the public were not involved in the design, or conduct, or reporting, or  
237 dissemination plans of our research proposal.

### 239 **List of abbreviations**

240 **PIGF-** placental growth factor

241 **PAPP-A-** pregnancy-associated plasma protein A

242 **AUC-** area under the curve

243 **LILACS-** Latin America and Caribbean Health Sciences Literature

244 **Scielo-** Scientific Electronic Library Online

245 **HTA-** Health Technology Assessment

246 **DARE-** Database of Abstracts of Reviews of Effects

247 **HMDB-** Human Metabolome Database

248 **QUADAS-2-** Quality Assessment of Diagnostic Accuracy Studies

249 **PRISMA-** Preferred Reporting Items for Systematic Reviews and Meta-Analysis

250 **HSROC-** Hierarchical summary receiver characteristic operating curve

251

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36 331 trimester urine and serum metabolomics for prediction of preeclampsia and gestational  
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40 335 PET, and IUGR. *Best Practice and Research: Clinical Obstetrics and Gynaecology.*  
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340



## 341 **Acknowledgements**

342 This is a modified version of the article that was part of the PhD thesis of Jussara de Souza  
343 Mayrink Novais presented to the Postgraduate Program on Obstetrics and Gynecology from  
344 the School of Medical Sciences of the University of Campinas, Brazil, under the tutorial of  
345 Jose Guilherme Cecatti and Maria Laura Costa on December 13<sup>th</sup> 2018.

## 346 **Authors' contributions**

347 JM worked out the protocol, developed searches and data management, will participate in  
348 selection, inclusion, quality assessment and data extraction of papers. DFBL helped working  
349 out the protocol and will participate in selection, inclusion, quality assessment and data  
350 extraction as well. MLC and JGC helped working out the protocol, and MLC will solve any  
351 disagreement concerning to the selected papers. JGC will supervise all the development of  
352 the systematic review. All authors read and approved this final manuscript.

## 353 **Funding**

354 This study is a sub product of the study "Preterm SAMBA" which was jointly financed by the  
355 Brazilian CNPq (CNPq, Grant 401636/2013-5) and the Bill and Melinda Gates Foundation  
356 (Grant OPP1107597).

## 357 **Competing interests**

358 The author(s) declare that they have not competing interests.

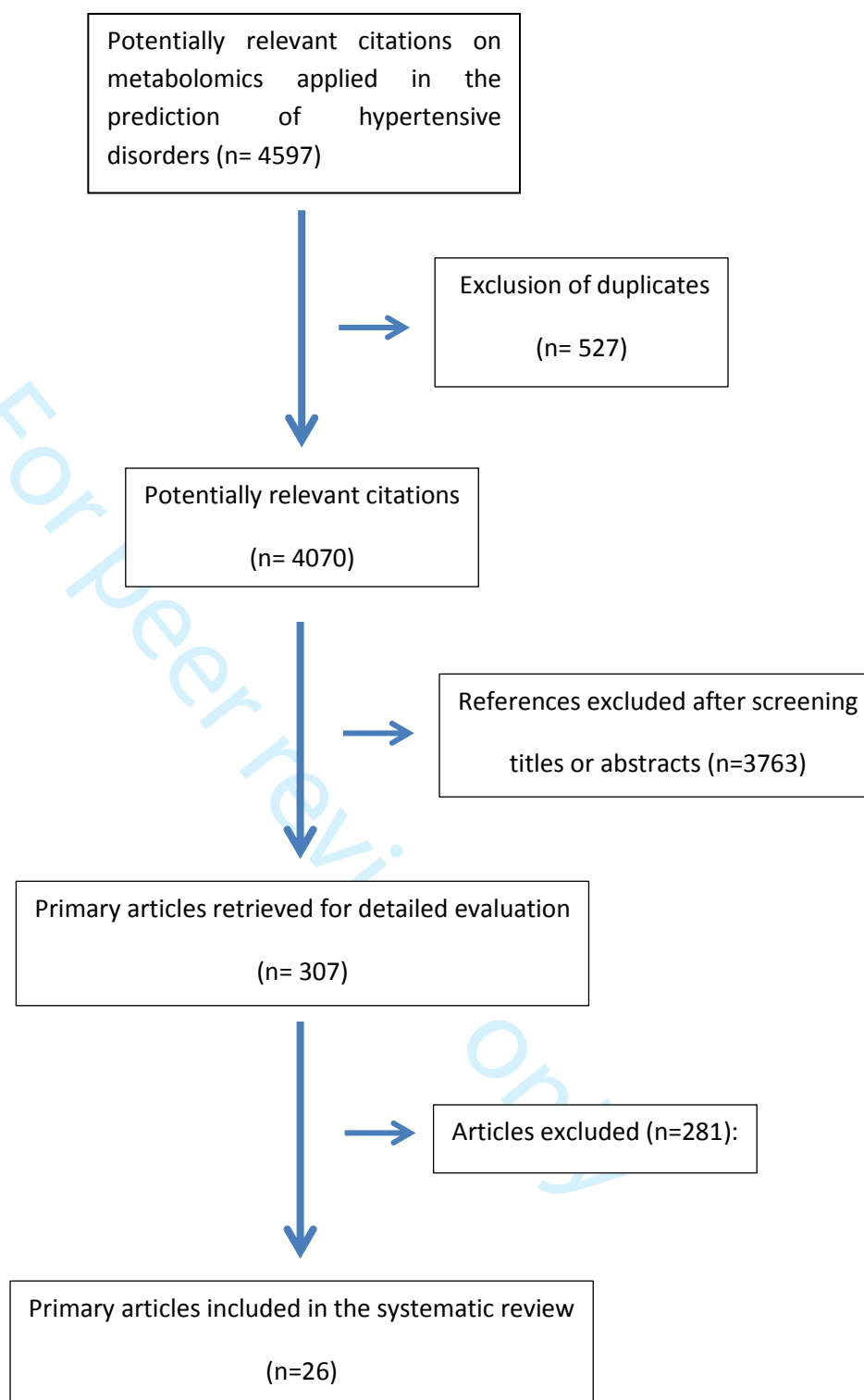
359 **Word count:** 1973 words

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## 361 **Figure Legend**

362 **Figure 1.** Flow chart of studies identified to be included in the systematic review.

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## PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted – Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	x <input type="checkbox"/>	<input type="checkbox"/>	3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	x <input type="checkbox"/>	
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	x <input type="checkbox"/>	<input type="checkbox"/>	52
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	x <input type="checkbox"/>	<input type="checkbox"/>	5,6,7,8
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x <input type="checkbox"/>	<input type="checkbox"/>	347-353
<b>Amendments</b>	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	x <input type="checkbox"/>	
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	x <input type="checkbox"/>	<input type="checkbox"/>	344-345
Sponsor	5b	Provide name for the review funder and/or sponsor	x <input type="checkbox"/>	<input type="checkbox"/>	344-345
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	x <input type="checkbox"/>	
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	x <input type="checkbox"/>	<input type="checkbox"/>	54-91

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	x <input type="checkbox"/>	<input type="checkbox"/>	94-99
<b>METHODS</b>					
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	x <input type="checkbox"/>	<input type="checkbox"/>	107-109; 128-132; 140-143
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	x <input type="checkbox"/>	<input type="checkbox"/>	104-107
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	x <input type="checkbox"/>	<input type="checkbox"/>	109-114
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	x <input type="checkbox"/>	<input type="checkbox"/>	121-122
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	x <input type="checkbox"/>	<input type="checkbox"/>	122-126
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	x <input type="checkbox"/>	<input type="checkbox"/>	184-191
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input type="checkbox"/>	x <input type="checkbox"/>	
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	x <input type="checkbox"/>	<input type="checkbox"/>	145-180
<b>Risk of bias in individual studies</b>	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	x <input type="checkbox"/>	<input type="checkbox"/>	193-204
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	x <input type="checkbox"/>	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau)	<input type="checkbox"/>	x <input type="checkbox"/>	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>	x <input type="checkbox"/>	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	x <input type="checkbox"/>	<input type="checkbox"/>	206-219

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	x <input type="checkbox"/>	
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	x <input type="checkbox"/>	

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# BMJ Open

## Metabolomics for prediction of hypertension in pregnancy: a systematic review and meta-analysis protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040652.R1
Article Type:	Protocol
Date Submitted by the Author:	23-Nov-2020
Complete List of Authors:	Mayrink, Jussara; Universidade Estadual de Campinas Faculdade de Ciencias Medicas Leite, Debora; State University of Campinas, Department of Tocogynecology; Universidade Federal de Pernambuco, Costa, Maria Laura Cecatti, Jose; State University of Campinas, Obstetrics and Gynecology
<b>Primary Subject Heading</b>:	Obstetrics and gynaecology
Secondary Subject Heading:	Epidemiology
Keywords:	Hypertension < CARDIOLOGY, Prenatal diagnosis < OBSTETRICS, EPIDEMIOLOGY

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## 1 SYSTEMATIC REVIEW PROTOCOL

2 **Metabolomics for prediction of hypertension in pregnancy: a systematic**  
3 **review and meta-analysis protocol**4  
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## 25 Abstract

26 **Introduction:** hypertension is a very important cause of maternal morbidity and mortality  
27 worldwide, despite efforts on prevention. The lack of a tool to provide effective and early  
28 prediction of hypertension for a high-risk group may contribute to improving maternal and  
29 fetal outcomes. Metabolomics has figured out as a promised technology to contribute to  
30 the improvement of hypertension in pregnancy prediction. **Methods and analysis:** our  
31 primary outcome is hypertensive disorders of pregnancy. A detailed systematic literature  
32 search will be performed in electronic databases PubMed, EMBASE, Scopus, Web of  
33 Science, Latin America and Caribbean Health Sciences Literature, Scientific Electronic  
34 Library Online, Health Technology Assessment, and Database of Abstracts of Reviews of  
35 Effects using controlled terms 'preeclampsia', 'hypertensive disorders', 'metabolomics' and  
36 'prediction' (and their variations). Studies from the latest twenty years will be included,  
37 except case reports, reviews, cross-sectional studies, letter to editors, expert opinions,  
38 commentaries papers or non-human research. If possible, we will perform a meta-analysis.  
39 Two peer reviewers will independently perform the search and in cases of discordance, a  
40 third reviewer will be consulted. **Ethics and dissemination:** as a systematic review, ethics  
41 approval is not required. The results of this review will present the current use and  
42 performance of metabolomics for predicting gestational hypertension. Such data could  
43 potentially guide future studies and interventions to improve existing prediction models.

### 44 Strengths and limitations of this study

- 45 • Electronic search will cover the most important current available scientific  
46 databases for health research;
- 47 • There will not be a language restriction;
- 48 • Considering the complexity of Metabolomics technology and its methods, there  
49 would be a limitation to perform a quantitative synthesis.

## 50 Keywords

1  
2  
3 51 Preeclampsia, pregnancy, hypertension, hypertensive disorders, hypertensive syndromes,  
4 52 metabolomics, metabolome

5  
6  
7 53 **Prospero register number: CRD42018097409**

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10  
11 54 **Introduction**

12  
13  
14 55 Hypertensive disorders in pregnancy consist of a group of conditions including  
15 56 preeclampsia, gestational hypertension, preeclampsia superimposed to chronic  
16 57 hypertension, white coat hypertension, masked hypertension and transient hypertension <sup>1</sup>  
17 58 <sup>2</sup>and appear as the second cause of maternal death in the world according to a study  
18 59 performed by the World Health Organization between 2003 and 2009 <sup>3</sup>. Preeclampsia is the  
19 60 leading cause of maternal morbidity and mortality in Brazil and several other low-and  
20 61 middle-income countries <sup>4,5</sup>. Its prevalence can vary according to the set of analyses, but  
21 62 the number ranges from 2 to 10% of all pregnancies <sup>4</sup>. Every year, around 70 thousand  
22 63 women die because of preeclampsia and its complications <sup>3</sup>, despite potential prevention  
23 64 implemented by low-dose aspirin <sup>6,7</sup>. This intervention can represent a reduction rate of  
24 65 around 50% in the incidence of the early-onset preeclampsia cases, which developed  
25 66 preeclampsia before 34 weeks of gestation <sup>7,8</sup>. In this scenario, the prediction of pregnant  
26 67 women under high-risk to develop preeclampsia is a key topic.

27  
28  
29 68 Some biomarkers have been proposed as earlier predictors (placental growth factor  
30 69 - PIGF, pregnancy-associated plasma protein A-PAPP-A) combined with clinical factors  
31 70 (pulsatility index of uterine arteries at Dopplervelocimetry exam, mean arterial blood  
32 71 pressure) in models with different detection and false-positive rates <sup>9-12</sup>. These studies  
33 72 present limitations regarding the number of participants enrolled and heterogeneity to

1  
2  
3 73 assess the prediction performance of those factors. Furthermore, the proposed prediction  
4  
5 74 models from combining those factors outline better detection rates for early-onset  
6  
7  
8 75 preeclampsia cases compared to late-onset cases <sup>13-15</sup>.  
9  
10

11 76 In the last decade, with the broad application of omics technologies, metabolomics  
12  
13 77 has been pointed as a promising tool for the identification of early predictors for many  
14  
15  
16 78 health disturbances <sup>16-18</sup> and preeclampsia is one of them. Through metabolomics, it would  
17  
18  
19 79 be possible to identify metabolites involved in the final line of gene expression and a  
20  
21 80 phenotypic signature in high resolution of the disease to be studied <sup>19-21</sup>. Studies have  
22  
23 81 provided some insights about preeclampsia prediction through metabolites, belonging to  
24  
25  
26 82 different chemical classes and showing different performances <sup>20-23</sup>. In 2010, Kenny et al  
27  
28 83 provided the initial knowledge on the topic, identifying 14 metabolites belonging to  
29  
30  
31 84 different chemical classes. When combined in an algorithm they showed a very good  
32  
33 85 performance, with an Area under the Curve (AUC) of 0.94 in a discovery phase of the study  
34  
35  
36 86 and a detection rate of 77%, considering a false-positive rate of 10% <sup>22</sup>. It represents a very  
37  
38 87 important tool option for prediction, especially concerning cases of late-onset  
39  
40  
41 88 preeclampsia, which are the majority and the most difficult cases to predict <sup>13-15</sup>. Thus, in  
42  
43 89 the sense of the inexistence of a systematic review protocol registered in this topic as well  
44  
45  
46 90 as a systematic review in progress or published, the main objective of this systematic review  
47  
48 91 is to determine the accuracy of metabolomics for predicting hypertensive disorders of  
49  
50  
51 92 pregnancy.  
52

53 93

#### 54 55 94 **Question formulation** 56 57

1  
2  
3 95 Because of the social and economic implication of hypertensive disorders, their  
4  
5 96 consequences to maternal and fetal lives worldwide and the lack of a useful screening test,  
6  
7  
8 97 in parallel to the increase of applicability of omics technologies, this systematic review will  
9  
10 98 be guided by this question: what is the performance of metabolomics for predicting  
11  
12 99 gestational hypertensive disorders? It is following the PICO method <sup>24</sup>and associated with  
13  
14  
15 100 the search strategy provided a preliminary flow chart of studies as summarized in figure 1.  
16  
17

18 101

## 102 **Methods and Analysis**

### 103 ***Search Strategy***

104 Electronic searches of literature will be carried out with these following databases: PubMed,  
105 EMBASE, Scopus, Web of Science, Latin America and Caribbean Health Sciences Literature  
106 (LILACS), Scientific Electronic Library Online (SciELO), Health Technology Assessment (HTA),  
107 Database of Abstracts of Reviews of Effects (DARE). We will include studies from the latest  
108 twenty years, considering that the vast majority of manuscripts on metabolomics are from  
109 this century. Our search strategy will combine terms with Boolean connectors related to  
110 the following categories: 1) hypertensive disorders, preeclampsia, pregnancy; 2)  
111 metabolomics, metabolome; and 3) screening, prediction. The Boolean connectors will be  
112 adapted according to the database used. We decided to use regular terms – not MESH or  
113 Emtree terms – taking into account the number of databases consulted, to use always the  
114 same terms for all of them. Also, we will search reference list of included articles, doing the  
115 backtracking of references. There will not be a language restriction. Before final publication,  
116 we will perform a new search in the databases to check if any study was published during

1  
2  
3 117 the period of the systematic review elaboration. The databases exploration process and its  
4  
5 118 results will follow the PRISMA Statement <sup>25</sup>.

7  
8 119 ***Study selection process***

9  
10 120 After searching all sources of databases cited above, all the citations will be exported into  
11  
12 121 EndNote® software. Firstly, two reviewers (JM and DFBL) will independently assess titles  
13  
14 122 and abstracts. Only papers considered potentially relevant according to the inclusion  
15  
16 123 criteria will be retrieved for further consideration. Cases of divergence will be analyzed by  
17  
18 124 a third reviewer (MLC) who will do the final decision. A fourth reviewer (JGC) will check all  
19  
20 125 procedures before approving the data extraction.

21  
22 126 ***Study inclusion criteria***

23  
24 127 Hypertensive disorders developed at any gestational age will be considered the domain  
25  
26 128 studied. Previous other chronic conditions (diabetes, renal diseases, etc.) will be reported  
27  
28 129 for stratification of analysis if the data allow for this. Original studies – including diagnostic  
29  
30 130 studies - involving pregnant women are the inclusion criteria, and congenital malformation  
31  
32 131 is the exclusion criteria.

33  
34 132 ***Interventions/exposure***

35  
36 133 Prediction of hypertensive disorders through metabolomics technologies is the intervention  
37  
38 134 to be studied. The biomarker analysis should have been performed on samples taken before  
39  
40 135 the hypertensive disorder diagnosis.

41  
42 136 ***Design***

43  
44 137 Our systematic review will include original studies (cohort or case-control studies), including  
45  
46 138 single or multiple pregnancies, as the studied population, and hypertensive disorders

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3 139 developed at any time of pregnancy, as the outcome of interest. We will exclude any studies  
4  
5 140 that are: cross-sectional studies, case reports, editorials, letter to editors, commentaries,  
6  
7  
8 141 expert opinions, any type of reviews, and experimental studies with animals, and when it is  
9  
10 142 not possible to extract the data about the outcomes of interest.

### 13 143 **Outcomes**

14  
15 144 We will include studies reporting outcomes of any hypertensive disorder developed during  
16  
17 145 pregnancy. Our primary outcome is preeclampsia, defined as the onset of hypertension  
18  
19 146 (systolic blood pressure of 140 mmHg or more and/or diastolic blood pressure of 90 mmHg  
20  
21 147 or more) after 20 weeks of gestation, measured at least in two different occasions,  
22  
23 148 combined with (1) proteinuria (300 mg/day or at least 1g/L [1+] on dipstick testing or spot  
24  
25 149 urine protein/creatinine>30mg/mmol [0.3mg/mg]) or (2) systemic complications or (3)  
26  
27 150 uteroplacental dysfunction (fetal growth restriction) <sup>1</sup>. By systemic complications, we will  
28  
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31  
32 151 consider:

- 33  
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35 152 ✓ Hematological complications (thrombocytopenia- platelet count below 150,000/dL,  
36  
37 153 disseminated intravascular coagulation, hemolysis);  
38  
39 154 ✓ Hepatic dysfunction (elevated transaminases – at least twice upper limit of normal +-  
40  
41 155 right upper quadrant or epigastric abdominal pain);  
42  
43 156 ✓ Neurological dysfunction (examples include eclampsia, altered mental status, blindness,  
44  
45 157 stroke or more commonly hyperreflexia when accompanied by clonus, severe  
46  
47 158 headaches when accompanied by hyperreflexia, persistent visual scotomata;  
48  
49  
50 159 ✓ Renal dysfunction (creatinine > 1.2mg/dL);  
51  
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53

54 160 Secondary outcomes include:  
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- 1  
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3 161 ✓ Early-onset preeclampsia: when occurs before or at 33 weeks of gestation <sup>26</sup>;  
4  
5 162 ✓ Late-onset preeclampsia: when occurs at or after 34 weeks of gestation <sup>26</sup>.  
6  
7  
8 163 ✓ Gestational hypertension: de novo development of high blood pressure after 20 weeks  
9  
10 164 of gestation (systolic blood pressure of 140 mmHg or more and/or diastolic blood  
11  
12 165 pressure of 90 mmHg or more), without any of the abnormalities that define  
13  
14 166 preeclampsia as discussed above <sup>1</sup>  
15  
16  
17 167 ✓ Whitecoat hypertension: it is demonstrated when normal blood pressure is registered  
18  
19 168 during 24 hours ambulatory monitoring in the first half of pregnancy <sup>1</sup>  
20  
21  
22 169 ✓ Preeclampsia superimposed on chronic hypertension: in a patient with high blood  
23  
24 170 pressure predating the pregnancy, it is registered the occurrence of preeclampsia <sup>1</sup>  
25  
26  
27 171 ✓ Masked hypertension: is characterized by blood pressure that is normal at office or clinic  
28  
29 172 but elevated at other times, most typically diagnosed by 24 hours ambulatory blood  
30  
31 173 pressure monitoring <sup>2</sup>  
32  
33  
34 174 ✓ Transient gestational hypertension is hypertension that arises in the second or third  
35  
36 175 trimester. The hypertension is detected in the clinic but then settles with repeated  
37  
38 176 blood pressure readings <sup>2</sup>  
39  
40  
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#### 178 **Data extraction**

179 Data will be extracted through a standardized data compilation form in duplicate to avoid  
180 errors. The variables of interest from each included study are: authors, country, year of  
181 publication, study design, number of participants, preeclampsia prevalence, gestational age  
182 of recruitment, biological samples utilized, laboratory methods, metabolomics technology

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3 183 applied and metabolites. The metabolites will be matched with the Human Metabolome  
4  
5 184 Database (HMDB) to check their biological function and chemical subclass. Missing data will  
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7  
8 185 be requested from study authors. Pairs of data-extraction forms will be checked for  
9  
10  
11 186 discrepancies.

### 12 13 187 **Quality Appraisal**

14  
15 188 The same two reviewers (JM and DFBL) who judged eligibility of papers will independently  
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17  
18 189 assess the risk of bias in included studies, but this time rating the methodological quality of  
19  
20  
21 190 the primary research. A third reviewer (MLC) will solve divergences when needed. Quality  
22  
23 191 Assessment of Diagnostic Accuracy Studies (QUADAS-2) is the standard scale to be applied  
24  
25 192 to assess internal validity<sup>27</sup>. This tool is composed of four domains: patient selection, index  
26  
27  
28 193 test (metabolomics technique), reference standard (arterial blood pressure) and flow and  
29  
30 194 timing of patient inclusion and follow up. Each domain is assessed in terms of risk of bias  
31  
32  
33 195 and the first three are assessed in terms of concerns regarding applicability. For each  
34  
35 196 domain, every study will be labelled as “low”, “high” or “unclear” risk of bias.

36  
37 197 Funnel plots and sensitivity and cumulative analyses will be applied for the detection  
38  
39  
40 198 of temporal trends and publication bias.

### 41 42 43 199 **Strategy for data synthesis**

44  
45 200 Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis  
46  
47  
48 201 (PRISMA), a flow diagram will be drawn<sup>25</sup>. Tables will show data regarding studies  
49  
50  
51 202 characteristics and risk of bias assessment for included and excluded studies. Narrative data  
52  
53 203 will be analyzed and structured according to the outcomes: preeclampsia, gestational  
54  
55 204 hypertension, transient gestational hypertension, white coat hypertension, masked



1  
2  
3 205 hypertension. If possible, we are going to perform subgroup analysis according to the  
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5 206 metabolomics methods applied: gas or liquid chromatography, coupled with mass  
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8 207 spectrometry, or proton nuclear magnetic resonance, and based on ethnic group and the  
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10  
11 208 severity of the hypertensive disease. We also intend to perform a sensitivity analysis based  
12  
13 209 on early and late preeclampsia cases if sufficient studies will be found.

14  
15 210 A meta-analysis will be performed (hierarchical summary receiver characteristic operating  
16  
17 211 curve, HSROC) and accuracy measures will be calculated depending on data availability. If a  
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19  
20 212 meta-analysis will be possible, considering the limitations imposed by data heterogeneity  
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22 213 and drawings of the vast majority of studies, we intend to use RevMan software. Taking into  
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24 214 account that the studies involve the frequency of metabolites and occurrence of  
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26 215 preeclampsia, we are going to use a fixed-effect model or random-effect model, depending  
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28 216 on the heterogeneity found. Heterogeneity will also be assessed, through the I-square test,  
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30 217 Hotelling's T-squared test and Cochran's Q test.  
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### 36 37 219 ***Ethics and dissemination***

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39 220 Prediction of hypertensive disorders has been studied over the years with specific  
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41 221 challenges. Among nulliparous for example, there is no history of previous events and a  
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43 222 previous history of preeclampsia, is considered the most consistent predictive risk factor <sup>28</sup>.  
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45 223 Another challenge to overcome is regarding late-onset preeclampsia cases, which represent  
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47 224 the majority of them. As cited above, the algorithms composed by biochemical and clinical  
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49 225 factors showed better results with early-onset cases of preeclampsia <sup>13-14</sup>.  
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3 226 Metabolomics is a very complex technology and it has emerged as a possibility for  
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5 227 prediction of adverse pregnancy outcomes <sup>29-31</sup>. The techniques employed are nuclear  
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8 228 magnetic resonance spectroscopy, gas or liquid chromatography-mass spectrometry,  
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10 229 Fourier transforms infrared spectrometry and capillary electrophoresis <sup>31</sup>. Because of this  
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13 230 complexity, results may be different concerning the metabolites found. Consequently,  
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15 231 generalizing results is also a challenge to overcome. This systematic review will contribute  
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18 232 to optimize the knowledge about the metabolites found in the studies and perhaps classify  
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20 233 them according to HMDB, enabling quality translational research.

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23 234 Besides, this systematic review will contribute to establishing the current state of  
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25 235 knowledge concerning the capacity of metabolomics to predict the occurrence of  
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27 236 preeclampsia. Taking into account that this outcome involves relevant consequences for  
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30 237 maternal and neonatal lives, the development of a tool that would predict preeclampsia is  
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32 238 essential. Furthermore, the results of this systematic review could be used to guide future  
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35 239 studies in this field. Once published, this systematic review will be freely available in an  
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37 240 open-access scientific journal.

#### 38 39 241 ***Patient and Public Involvement***

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42 242 Patients or the public were not involved in the design, or conduct, or reporting, or  
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44 243 dissemination plans of our research proposal.

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#### 47 245 **List of abbreviations**

48  
49 246 PIGF- placental growth factor

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51 247 PAPP-A- pregnancy-associated plasma protein A

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53 248 AUC- area under the curve

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55 249 LILACS- Latin America and Caribbean Health Sciences Literature

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3 250 Scielo- Scientific Electronic Library Online  
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5 251 HTA- Health Technology Assessment  
6  
7 252 DARE- Database of Abstracts of Reviews of Effects  
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9 253 HMDB- Human Metabolome Database  
10  
11 254 QUADAS-2- Quality Assessment of Diagnostic Accuracy Studies  
12  
13 255 PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analysis  
14  
15 256 HSROC- Hierarchical summary receiver characteristic operating curve  
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17 257

### 18 258 **Acknowledgements**

19 259 This is a modified version of the article that was part of the PhD thesis of Jussara de Souza  
20 260 Mayrink Novais presented to the Postgraduate Program on Obstetrics and Gynecology from  
21 261 the School of Medical Sciences of the University of Campinas, Brazil, under the tutorial of  
22 262 Jose Guilherme Cecatti and Maria Laura Costa on December 13<sup>th</sup> 2018.

### 23 263 **Authors' contributions**

24 264 JM worked out the protocol, developed searches and data management, will participate in  
25 265 the selection, inclusion, quality assessment and data extraction of papers. DFBL helped  
26 266 working out the protocol and will participate in selection, inclusion, quality assessment and  
27 267 data extraction as well. MLC and JGC helped working out the protocol, and MLC will solve  
28 268 any disagreement concerning the selected papers. JGC will supervise all the development  
29 269 of the systematic review. All authors read and approved this final manuscript.

### 30 270 **Funding**

31 271 This study is a sub-product of the study "Preterm SAMBA" which was jointly financed by the  
32 272 Brazilian CNPq (CNPq, Grant 401636/2013-5) and the Bill and Melinda Gates Foundation  
33 273 (Grant OPP1107597).

### 34 274 **Competing interests**

35 275 The author(s) declare that they have not competing interests.

36 276 **Word count:** 2031 words

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5 278 **Figure Legend**

6  
7 279 **Figure 1.** Flow chart of studies identified to be included in the systematic review.  
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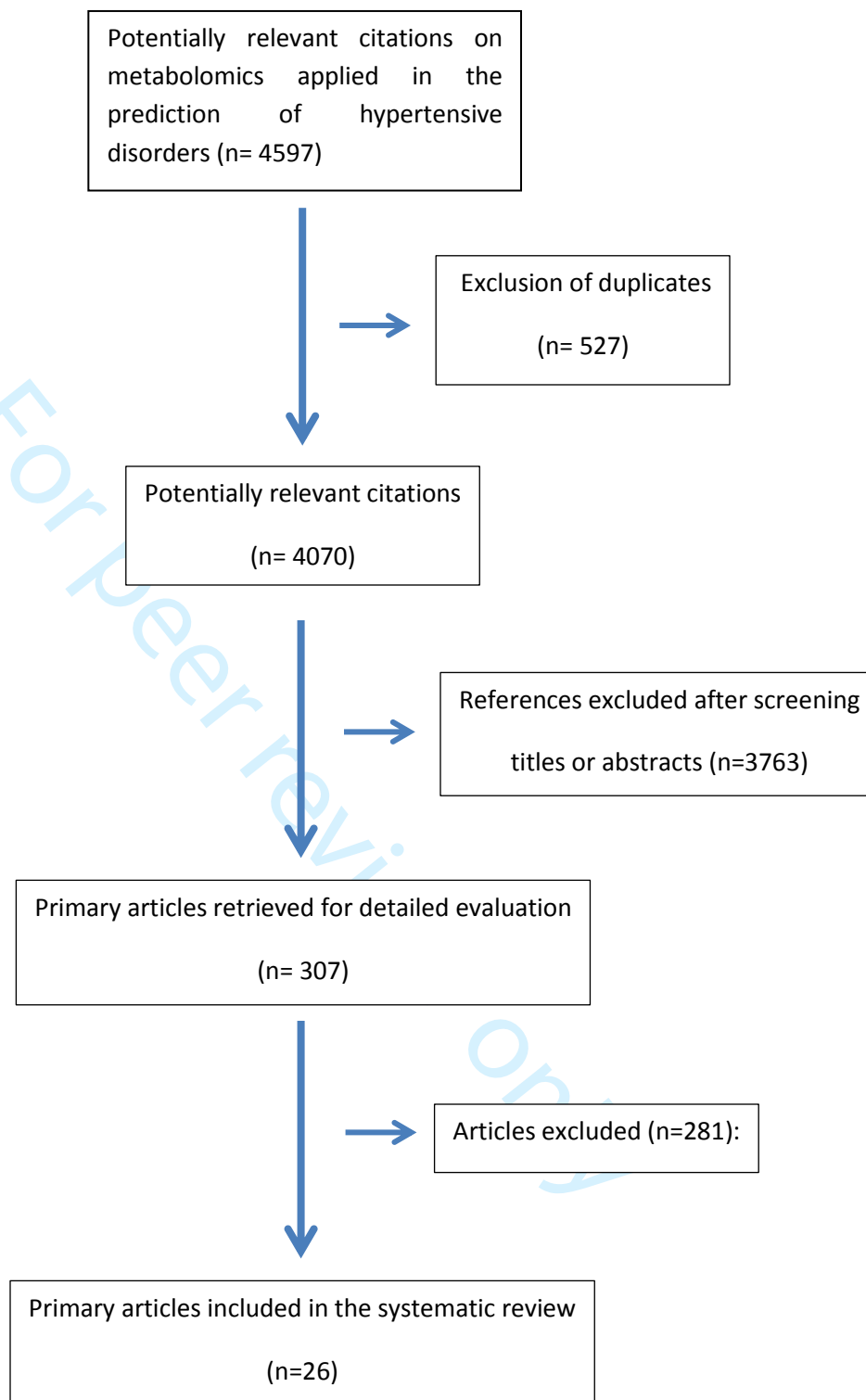
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## PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted – Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	x <input type="checkbox"/>	<input type="checkbox"/>	3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	x <input type="checkbox"/>	
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	x <input type="checkbox"/>	<input type="checkbox"/>	52
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	x <input type="checkbox"/>	<input type="checkbox"/>	5,6,7,8
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	x <input type="checkbox"/>	<input type="checkbox"/>	347-353
<b>Amendments</b>	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	x <input type="checkbox"/>	
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	x <input type="checkbox"/>	<input type="checkbox"/>	344-345
Sponsor	5b	Provide name for the review funder and/or sponsor	x <input type="checkbox"/>	<input type="checkbox"/>	344-345
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	x <input type="checkbox"/>	
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	x <input type="checkbox"/>	<input type="checkbox"/>	54-91

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	x <input type="checkbox"/>	<input type="checkbox"/>	94-99
<b>METHODS</b>					
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	x <input type="checkbox"/>	<input type="checkbox"/>	107-109; 128-132; 140-143
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	x <input type="checkbox"/>	<input type="checkbox"/>	104-107
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	x <input type="checkbox"/>	<input type="checkbox"/>	109-114
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	x <input type="checkbox"/>	<input type="checkbox"/>	121-122
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	x <input type="checkbox"/>	<input type="checkbox"/>	122-126
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	x <input type="checkbox"/>	<input type="checkbox"/>	184-191
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input type="checkbox"/>	x <input type="checkbox"/>	
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	x <input type="checkbox"/>	<input type="checkbox"/>	145-180
<b>Risk of bias in individual studies</b>	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	x <input type="checkbox"/>	<input type="checkbox"/>	193-204
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	x <input type="checkbox"/>	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau)	<input type="checkbox"/>	x <input type="checkbox"/>	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>	x <input type="checkbox"/>	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	x <input type="checkbox"/>	<input type="checkbox"/>	206-219

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	x <input type="checkbox"/>	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	x <input type="checkbox"/>	

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