Clinical risk factors for preeclampsia determined in early pregnancy: a systematic review and meta-analysis of large cohort studies

Running title: Clinical risk factors for preeclampsia in early pregnancy

Emily Bartsch, BMSc
emily.bartsch@mail.utoronto.ca
University of Toronto
Toronto, Canada

Karyn Medcalf, HBSc
karyn.medcalf@mail.utoronto.ca
University of Toronto
Toronto, Canada

Alison L. Park, MSc
alison.park@ices.on.ca
Institute for Clinical Evaluative Sciences
Toronto, Canada

Joel G. Ray, MD MSc FRCP
rayj@smh.ca
Departments of Medicine, Health Policy Management and Evaluation, and Obstetrics and Gynecology
St. Michael’s Hospital, University of Toronto
Toronto, Canada

On behalf of the High Risk of Preeclampsia Identification Group *

Contact:
Joel G Ray
Department of Medicine, St. Michael’s Hospital
30 Bond Street
Toronto, Ontario, M5B 1W8
Tel: (416) 864-6060, Ext 77442
Fax: (416) 864-5485
e-mail: rayj@smh.ca

ABSTRACT COUNT: 310
MAIN WORD COUNT: 4066

*Members are listed at the end of this article.

Keywords: preeclampsia; aspirin; risk threshold; event rate; number needed to treat
Abstract

Objective: Clinical practice guidelines recommend ASA at 12 to 16 weeks in women at “high risk” of preeclampsia (PE), but lack a systematic approach to identify these women in early pregnancy. Accordingly, we developed a practical evidence-based list of clinical risk factors (RFs) that can be assessed by a clinician at ≤ 16 weeks to estimate a woman’s risk of PE.

Design: Systematic review and meta-analysis of cohort studies.


Eligibility criteria for selecting studies: Cohort studies with ≥ 1000 participants, that evaluated the risk of PE in relation to a common and generally accepted clinical RF assessed at ≤ 16 weeks’ gestation.

Data extraction: Two independent reviewers extracted data from included studies. A pooled event rate and pooled relative risk (RR\textsubscript{pooled}) for PE were calculated for each of 14 RFs.

Results: We included 25,356,688 pregnancies among 92 studies. The RR\textsubscript{pooled} for each RF significantly exceeded 1.0, except for prior IUGR. Women with antiphospholipid antibody syndrome (aPL) had the highest pooled rate of PE (17.3%, 95% CI 6.8 to 31.4). Those with prior PE had the greatest RR\textsubscript{pooled} for PE (8.4, 95% CI 7.1 to 9.9). Chronic hypertension ranked second, both in terms of its pooled rate (16.0%, 95% CI 12.6 to 19.7) and RR\textsubscript{pooled} (5.1, 95% CI 4.0 to 6.5) of PE. Pregestational diabetes (pooled rate 11.0%, 95% CI 8.4 to 13.8; RR\textsubscript{pooled} 3.7, 95% CI 3.1 to 4.3), pre-pregnancy BMI > 30 kg/m\textsuperscript{2} (7.1%, 95% CI 6.1 to 8.2; RR\textsubscript{pooled} 2.8, 95% CI 2.6 to 3.1) and use of assisted reproductive technology (6.2%, 95% CI 4.7 to 7.9; RR\textsubscript{pooled} 1.8, 95% CI 1.6 to 2.1) were other prominent RFs.

Conclusions: We identified several practical clinical RFs that, either alone or in combination, might identify women in early pregnancy who are at “high risk” of PE. These data can inform the generation of a clinical prediction model for PE and the use of ASA prophylaxis in pregnancy.
INTRODUCTION

Preeclampsia (PE) is a common condition of pregnancy, marked by the onset of hypertension and proteinuria[1, 2]. At least 75 randomized controlled trials (RCTs) have shown that antiplatelet agents – especially aspirin (ASA) – effectively and safely prevent PE among women at moderate or high risk of developing the condition[3-5]. Meta-analyses have shown a 53% (95% confidence interval [CI] 35 to 66) relative risk reduction (RRR) for PE when ASA is started at 12 to 16 weeks gestation among high-risk women[6-8]. Internationally-published clinical practice guidelines strongly recommend that physicians and midwives start ASA in women at high risk of PE[9-11]. These guidelines suggest choosing from a list of single risk factors (RF) to identify women at high risk of PE, or from a combination of moderate RFs, but the derivation of this partial list was neither systematic nor based on clinical risk factors (RFs) that are available up to 16 weeks gestation. Focusing on those at high risk of PE avoids treating healthy women, who gain little or no benefit from ASA prophylaxis[9, 12-14].

Many RCTs of ASA prophylaxis did not describe their criteria used to define a woman as high risk, and others used abnormal uterine artery Doppler ultrasonography, which has limited sensitivity, is rarely done before 16 weeks, and has limited availability among midwives and family practitioners[15]. Other studies have proposed several RFs to characterize women at high risk of PE, including nulliparity, older age, chronic hypertension and pre-pregnancy diabetes mellitus[15, 16], yet, again, the absolute and relative importance of one RF over another has not been systematically assessed.

Given the limitations and variability in the current criteria used to identify women at high risk of PE, there is a need for a clear, concise and evidence-based list of indicators to estimate a woman’s risk of PE. These indicators should consider prior pregnancy events as well as current pregnancy factors that can be efficiently gathered at an early prenatal visit. In order to generate this list, we completed a meta-analysis of large cohort studies of one or more RFs for PE. Our approach enabled us to generate three practical estimates, as study objectives: 1) The absolute risk of developing PE in the presence vs. absence of a given RF; 2) the relative risk (RR) of developing PE in the presence vs. absence of a given RF; and 3) the population attributable fraction (PAF) for PE in relation to each RF. The first two metrics are useful to clinicians, and the third metric can help guide public health policy at the population level. Finally, we outlined how our generated list of individual RFs might be applied to identify “high risk” women, such as those who may benefit from ASA prophylaxis.
METHODS

Search strategy

We searched PubMed and Embase, restricting our query to publications in English, with abstracts available, from the year 2000 to June 2015. The PubMed and Embase search strategies are shown in Supplemental file 1.

Selection of studies

We identified publications investigating the association between PE and at least one prior pregnancy or current pregnancy RF. We examined those RFs described in the published guidelines and reviews[13-19], that were patient specific, readily recalled by a woman or abstracted from her prior pregnancy record, and that a general clinician could ascertain in the first trimester of pregnancy. For these reasons, and the observation that a family history in risk assessment tends to have a low sensitivity (i.e., low recall)[20], we did not assess family history of PE as a RF. We also limited our selection to large sample cohort studies because they tend to be more representative of the general population than small single-centre studies, and they have sufficient statistical power to assess less prevalent, but potentially important, RFs[21].

Selected prior pregnancy RFs were a history of any of the following arising within a previous pregnancy:

- PE
- Placental abruption
- Fetal intrauterine growth restriction (IUGR)
- Stillbirth.

Current pregnancy RFs were any of the following early within the current pregnancy:

- Nulliparity
- Advanced maternal age
- High body mass index (BMI)
- Chronic hypertension
- Pre-pregnancy diabetes mellitus (type 1 or type 2),
- Chronic kidney disease
- Systemic lupus erythematosus (SLE)
- Antiphospholipid antibody syndrome (aPL)
• Assisted reproduction (ART)
• Multifetal pregnancy.

The resulting papers were first screened by title and abstract. Full-text articles were obtained that met all of the following screening criteria:

1) A cohort study design with a minimum sample size of 1000 pregnancies;
2) The study evaluated the relation between one or more of the aforementioned RFs and the outcome of PE;
3) The authors provided the number of PE events among their participants with and without a given RF, to enable the calculation of pooled effect sizes, as described below.

Full-text papers were included in the final dataset if they still met the aforementioned screening criteria, and additionally met the following criterion:

4) The study evaluated each RF up to 16 weeks gestation or earlier (since ASA might be more efficacious when initiated before this gestational age[6-8]).

Study screening and data abstraction were performed by two authors (EB and KM), both of whom are student physicians, in which EB screened all citations retrieved from the database searches, and EB and KM evaluated the eligibility of the full-text articles. Disagreements were resolved by discussion or in consultation with a third author (JGR). If two published studies evaluated the same cohort of women, then we included that with the largest number of women or the greatest number of relevant outcomes. Study authors were not contacted.

Data abstraction from eligible studies

Data abstraction was independently conducted by two reviewers (EB and KM), using standardized tables. The first table considered the characteristics of each study, such as setting, inclusion/exclusion criteria, sample size, and the definition of PE. In a second table, we recorded the proportion of women who developed PE in the presence (i.e. \( n_p/N_p \)) vs. absence (i.e. \( n_{ue}/N_{ue} \)) of each given RF. We then generated an unadjusted relative RR for each RF in each study. When available, we also recorded the fully adjusted RR, hazard ratio (HR) or odds ratio (OR) that was provided by the study authors for each respective RF.
Data analysis

For each RF, we first calculated the pooled PE event rate in the exposed and unexposed groups, using an arcsine transformation. As statistical heterogeneity was evident across studies, we used a DerSimonian-Laird binary random-effects model to derive a pooled RR (RR_{pooled}) and 95% CI for each RF. For the calculated RR_{pooled} for each RF, heterogeneity was assessed by the I^2 measure.

Using the RR_{pooled} values, we calculated the population attributable fraction (PAF) for each RF, calculated using the following formula:

\[
PAF = \frac{P_{epooled}(RR_{pooled} - 1)}{P_{epooled}(RR_{pooled} - 1) + 1},
\]

where \(P_{epooled}\) is the number of women with a given RF in each study divided by the total number of women in that same study, pooled across studies using the arcsine transformation, and where RR_{pooled} is the RR_{pooled} calculated above. We used OpenMeta[Analyst] (Providence, RI) for all meta-analyses.

We performed three additional analyses that were limited to three chosen RFs, namely prior PE (representing a RF arising in a prior pregnancy), chronic hypertension (a RF identified in the current pregnancy) and pre-pregnancy BMI > 30 kg/m^2 (a RF measured early in the current pregnancy). Each of these RFs had a sufficient number of studies to enable these further analyses. First, in a sensitivity analysis, we re-calculated the RR_{pooled} using data limited to prospective studies, which tend to have more accurate ascertainment of RFs and outcomes, and also less biased effect sizes[22]. Second, we constructed three funnel plots to assess publication bias. Third, in a post hoc analysis, we determined the agreement between our calculated crude RR values and the adjusted RR values originally published in each study, expressed as an R^2 and 95% CI. If adjusted ORs were originally presented, then adjusted RR values were derived using the formula provided by Zhang and Yu[23].

Sinclair and colleagues previously described the threshold number needed to treat (NNT_\text{T}) and minimum event rate for treatment (MERT)[24]. MERT – the minimum disease event rate that justifies offering a given treatment – is a function of both the NNT_\text{T} and the RRR (i.e., efficacy) conferred by the treatment. We adapted their approach[24] to calculate the threshold number needed to prevent (NNP_\text{T}) with ASA in the presence of a given PE RF – that is, the maximum number of women with the RF in whom one would be willing to give ASA in order to prevent one case of PE, using the following formula:

\[
NNP_\text{T} = \frac{1}{EER*RRR},
\]

where EER is the pooled event rate of PE in the exposed group as calculated above for each RF, and where RRR is the established efficacy of ASA, with reported RRRs of 10%, 30% or 50% in various meta-analyses[3-5]. We previously showed that a conservative estimate of the NNP_\text{T} for ASA prophylaxis is about 250 women, assuming a modest gain of 0.05 quality-adjusted life years (see
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4366221/figure/pone.0116296.g001/ in our prior study[25]). If a RF on its own was shown to have a NNP_{R} under 250, especially at a small RRR of 10%, then it might influence one’s decision to start ASA prophylaxis.

**Patient involvement**

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

**RESULTS**

The selection process for articles included in our systematic review and meta-analysis is depicted in Figure 1. There were 4048 non-duplicate, potentially relevant citations (Supplemental file 1). Of these, 208 publications met the screening criteria, and, after review of the full-text articles, a total of 92 articles met our inclusion criteria and were included herein[26-117] (Supplemental file 2).

**Characteristics of included studies**

Supplemental file 2 shows the general study characteristics and sample characteristics of the included studies, comprising 25,356,688 pregnancies in 27 different countries. There were 40 studies from Europe, and 30 studies from North America. Of the 92 studies, 55 were retrospective and 37 were of a prospective cohort design. There were 61 studies that used a standard clinical definition of PE, 16 that used International Statistical Classification of Diseases and Related Health Problems (ICD) codes, while 15 studies provided no formal definition of PE. The mean (SD) number of participants was 275,616 (704,906), with a minimum of 1043 and a maximum of 4,395,968. 57 studies (62.0%) were limited to singleton pregnancies, while out of 92 studies, 9 (9.8%) excluded stillbirths and 18 (19.6%) excluded congenital anomalies. There were 24 studies that documented participant attrition, which was about 3%, on average (Supplemental file 2).

**Quantitative data synthesis**

The pooled PE event rates in the exposed and unexposed groups, according to each RF, are shown in Figure 2. In the unexposed groups, for each specific RF, the pooled PE event rate was always under 5%.
The weighted mean (SD) pooled PE event rate for all RFs was 2.7% (0.93) across all unexposed groups, in contrast to a weighted mean (SD) rate of 7.3% (4.6) across all exposed groups.

The RR_{pooled} for each RF was significantly greater than 1.0, with the exception of a history of prior IUGR, which was based on one study comprising 55,542 participants (Figure 2 and Supplemental file 3). Although women with aPL had the highest pooled rate of PE (17.3%, 95% CI 6.8 to 31.4), those with prior PE had the greatest RR_{pooled} (8.4, 95% CI 7.1 to 9.9). Chronic hypertension ranked second, both for the pooled rate (16.0%, 95% CI 12.6 to 19.7) and RR_{pooled} (5.1, 95% CI 4.0 to 6.5) of PE. As indicated by the I^2 values, there was a high level of heterogeneity for the RR_{pooled} for most RFs (Figure 2). The definition of chronic hypertension varied by study: for example, Anderson et al.[28] defined chronic hypertension as hypertension before 20 weeks gestation or a medical history of essential hypertension, while Basso et al.[30] defined it as self-reported pre-existing hypertension, while Magnussen et al.[71] used a measured pre-pregnancy blood pressure above 140/90 mmHg. When we examined studies of chronic hypertension, the pooled rate of PE was 16.0% (95% CI 15.2 to 16.7) among women with chronic hypertension in studies which PE was based on a standard clinical definition, compared to 5.9% (95% CI 5.7 to 6.2) among women with chronic hypertension in studies which PE was based on ICD coding. However, in the same studies, among women without hypertension, the respective pooled rates of PE were 3.1% (95% CI 3.1 to 3.1) and 2.7% (95% CI 2.7 to 2.7). Likewise, in women whose BMI was ≥ 30 kg/m^2 the pooled rate of PE was 5.1% (95% CI 5.0 to 5.2) using ICD coding versus 7.7% (95% CI 7.6 to 7.8) using a standard clinical definition, contrasted by respective pooled PE rates of 2.0% (95% 2.0 to 2.0) and 2.8% (95% CI 2.7 to 2.8) in women with BMI < 30 kg/m^2.

Nulliparity had the greatest PAF for PE (32.3%, 95% CI 27.4 to 37.0), followed by pre-pregnancy BMI > 25 kg/m^2 (23.8%, 95% CI 22.0 to 25.6) and prior PE (22.8%, 95% CI 19.6 to 26.3) (Figure 3). aPL had one of the lowest PAFs (0.18%, 95% CI 0.079 to 0.33).

**Additional analyses**

In the sensitivity analysis limited to prospective cohort studies, the RR_{pooled} for prior PE (7.4, 95% CI 5.9 to 9.5), chronic hypertension (5.4, 95% CI 4.2 to 7.0) and pre-pregnancy BMI >30 kg/m^2 (2.7, 95% CI 2.5 to 2.9) did not appreciably differ from the RR_{pooled} based on prospective and retrospective cohort studies together (Figure 2).

The funnel plot for each of the three RFs was generally symmetrical, but contained many points outside of the pseudo 95% CIs, especially at very low standard errors (Supplemental file 4).
In the post hoc analysis, the $R^2$ agreement between our calculated crude RRs and the originally-published adjusted RRs was 0.81 (95% CI 0.60 to 1.00) for prior PE, 0.78 (95% CI 0.54 to 1.00) for chronic hypertension, and 0.75 (95% CI 0.58 to 0.91) for pre-pregnancy BMI > 30 kg/m$^2$.

Application of findings to identify “high risk” women who may benefit from ASA prophylaxis

The NNP$_T$ (upper 95% CI) for ASA prophylaxis to prevent one case of PE varied by RFs and by the expected efficacy of ASA (Figure 4). Considering each RF and its pooled PE event rate, and assuming a conservative 10% RRR conferred by ASA, we found that aPL, chronic hypertension, prior PE, pre-gestational diabetes mellitus, pre-pregnancy BMI > 30 kg/m$^2$ and assisted reproductive technology (ART) each had an NNP$_T$ whose upper 95% CI was well below the clinically important NNP$_T$ of 250 (Figure 4, red dashed line). At a 30% and 50% RRR, the remaining RFs were below the NNP$_T$ of 250, with the exception of SLE and prior IUGR (Figure 4).

DISCUSSION

Main findings

Based on a body of large-sample cohort studies, we estimated the contributions of several clinical RFs to developing PE, considering the absolute rate and RR of PE – metrics understood by clinicians – and also on the PAF – a metric applicable to public health initiatives at the population level. Except for a history of IUGR, each identified RF was associated with a significantly heightened risk of PE. Some RFs, including aPL, prior PE, chronic hypertension, pre-gestational diabetes and BMI > 30 kg/m$^2$, were also strongly associated with a high rate of PE. We used the example of ASA prophylaxis to demonstrate how these RFs can inform a PE prevention program.

Strengths and limitations

We pooled data from studies of more than 25 million women, enabling us to systematically evaluate several well-defined RFs that have been largely accepted in most clinical settings and within published clinical practice guidelines[9-11]. Our inclusion of only large sample cohort studies helped curtail the bias potentially introduced by smaller studies[21], but by no means eliminated the risk of participant selection bias. Many of the cohort studies included herein were population-based (Supplemental file 2), thereby avoiding small audit-based or single-centre studies that could be more prone to selection bias. When we limited our analysis to prospective cohort studies, which tend to have less selection bias, the RR$_{pooled}$ did not differ appreciably from those in the main analysis. Our determination of the risk of PE
was better informed for some RFs than for others (e.g., prior IUGR or SLE), which were based on only one or two contributing studies and a fewer overall number of participants. Other RFs (e.g., maternal age > 40 years) were evaluated based on a sufficient number of studies and pregnancies, but still surpassed the NNP$_T$ of 250. Family history of PE was not evaluated herein, for reasons stated above[20], but it is certainly worthy of additional exploration as a RF for PE.

By restricting to studies examining RFs determined in early pregnancy, we focused on RFs that could lead to a timely intervention, such as ASA prophylaxis[6-8]. We generated reliable and consistent results across studies, since the majority were completed in the past two decades, within Western nations, and approximately two-thirds of studies used a standard clinical definition of PE. This was evidenced by a 2.7% weighted mean PE event rate for all RFs across all unexposed groups, a figure close to that estimated within Western countries[118]. Certainly, in low-income countries, where the rate of PE tends to be higher[1, 2] and the prevalence of RFs may differ, less can be said about the behaviour of the currently evaluated RFs for PE.

As a limitation, 15 out of 92 studies did not provide a formal definition of PE, the main outcome herein. When the outcome of PE was based on a standard clinical definition, the rate of PE was much higher than PE rates based on ICD coding, as noted for women with chronic hypertension and women with a BMI ≥ 30 kg/m$^2$. Another inconsistency was in the differing definitions of certain RFs. “Renal disease”, for example, ranged from a mild to severe loss of renal function. Similarly, the definition of chronic hypertension or aPL would certainly vary by study and/or era. Notwithstanding that limitation, aPL and chronic hypertension were apparent individual RFs for PE, and chronic kidney disease was likely the same. Certainly, varying definitions of a given RF and/or PE could produce heterogeneity in our associated risk estimates. Moreover, since several included large population-based cohort studies relied on ICD coding for RFs and PE, their influence would be expected to underestimate the pooled PE event rates or the RR$_{pooled}$ for a given RF and PE. In addition, some RFs may heighten the risk of PE in a dose-response manner. Therefore, dichotomizing those RFs may be inappropriate. For instance, a woman whose BMI is 29 kg/m$^2$ may have a risk of PE that is comparable to a woman whose BMI is 31 kg/m$^2$. Our funnel plots showed a small degree of asymmetry, which would suggest publication bias. However, it can be difficult to assess publication bias when effect sizes are highly heterogeneous[119], as was the case herein. Moreover, our use of a random-effects model may explain why many points in the funnel plots were outside of the pseudo 95% CIs[120] (Supplemental file 4). We observed a high level of heterogeneity for the RR$_{pooled}$ values. However, some degree of heterogeneity is to be expected, and may actually increase the generalizability of a meta-analysis over single studies[121].
In meta-analyses of observational studies, variation can be due to measurement bias, selection bias, confounding and differences in effect modification[122]. While only 24 of 92 studies described participant attrition, the average rate was just 3%, suggesting that attrition is uncommon in obstetrical studies, where the duration of follow-up is typically under 40 weeks. In our analyses, we used bivariate data to calculate the pooled event rates, $RR_{\text{pooled}}$, and PAF. Accordingly, we could not account for the interaction between one RF and another. For prior PE, chronic hypertension and pre-pregnancy BMI > 30 kg/m², we found good agreement between the calculated unadjusted RRs and the reported adjusted RRs. In addition, our calculated rate of PE in women with prior PE based on aggregate data (12.0%, 95% CI 10.4 to 13.7) was similar to that in a recent meta-analysis using individual patient data (13.8%, 95% CI 13.6 to 14.1)[123]. None of the RFs evaluated herein would be particularly susceptible to recall bias, especially those that were measured in the current pregnancy. Even for the RF of prior PE, cohort studies have observed a sensitivity of 73% to 87% and a specificity greater than 95% for recalling the condition at some later period[124]. While this offers some degree of re-assurance that our current analytical approach provided precise and unbiased estimates of the rate of PE, a meta-analysis of individual patient data from cohort studies and randomized clinical trials (e.g., of ASA prophylaxis[13]) could assess the veracity of this statement.

**Interpretation**

By quantifying the risk of PE conferred by various individual clinical RFs, a clinician may be better equipped to estimate a woman’s risk of PE, and her candidacy for heightened surveillance or prophylactic measures, including ASA. Additionally, our findings could enhance the choice and weighting of first-trimester clinical factors in future clinical prediction models for PE[125].

At a population health level, the PAFs calculated herein suggest a different line-up of priority RFs for PE, and only some of which are modifiable (Figure 3). For example, nulliparity is not reversible, while pre-pregnancy obesity is. Moreover, as obesity is closely linked to chronic hypertension[126], a reduction in pre-pregnancy BMI could reduce both of these important RFs for PE. Certainly, in women with non-modifiable RFs, such as a prior history of PE, one may consider alternative strategies. The example we used herein was ASA prophylaxis, which has been shown to efficaciously and safely reduce the risk of PE in high-risk women[9, 14]. Some RFs – aPL, chronic hypertension, prior PE, pregestational diabetes mellitus, pre-pregnancy BMI > 30 kg/m² and ART – were each found to have a high rate of PE and a low NNP₁, which would justify consideration for ASA (Figure 4). Outside of pregnancy, for example, 420 adult women need to be treated with ASA over five years to prevent one cardiovascular event[127].
Herein, we adopted a much more conservative approach, setting the NNP\textsubscript{T} at 250, knowing that women only need to take ASA for 25 weeks to prevent a single case of PE. It is on this basis that certain RFs, either alone or in combination, might be enough to label a woman as being at “high risk” for PE. For others, we either lacked confidence about their role as a distinct RF for PE, or they simply surpassed NNP\textsubscript{T} of 250. Notwithstanding, we feel that all of the RFs studied herein should be evaluated within a multivariable model examining the risk of PE, with various combinations of RFs. For prior IUGR, itself a heterogeneous state\cite{128}, its role as a PE RF remains to be determined, using a standard and specific definition.

The main goal of this meta-analysis was to identify those clinical RFs that serve as potential determinants of PE. Schnohr and colleagues used a similar approach while ranking the top-10 RFs for coronary heart disease\cite{129}. They found that their prioritization of RFs differed at the individual patient level (based on the RR) from that at the population level (based on the PAF)\cite{129}. This dual approach is attractive, as a woman with a rare RF like aPL is certainly at high risk of PE in the presence of that RF (Figure 2), even though the rarity of that RF makes it less of a consideration when attempting to reduce PE risk within the entire population (Figure 3). Moreover, they used a multivariable approach in their analysis of RFs for coronary heart disease, something to be considered in comparing the influence of RFs for PE.

CONCLUSION

We identified the extent to which various clinical RFs in early pregnancy heighten a woman’s absolute and relative risk for PE. Some of the major RFs evaluated herein produced PE event rates that were either similar to, or lower than, the rates seen in RCTs of ASA prophylaxis among women at risk of PE\cite{13-19} (Supplemental file 5). Accordingly, evaluating whether the efficacy (i.e., RRR) of ASA prophylaxis differs across RFs can clarify whether they are equally responsive to that, or other, interventions. Additionally, evaluating the effectiveness of ASA in the prevention of preterm PE and severe forms of PE, by individual RFs and their combination, is needed. Separately, there is evidence that clinical decisions are viewed differently by a patient and her health care provider\cite{130}, as does their perception of risk\cite{131, 132}. Thus, data should be obtained from the patient and practitioner on the NNP\textsubscript{T} at which they are comfortable initiating ASA prophylaxis.
Details of ethics approval

None required as no original data were used herein.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contribution to Authorship

- Bartsch: study concept, analysis and interpretation of the data, drafting of manuscript, manuscript revision, approval of final version, guarantor.
- Medcalf: analysis and interpretation of the data, manuscript revision, approval of final version
- Park: analysis and interpretation of the data, manuscript revision, approval of final version
- Ray: study concept, analysis and interpretation of the data, drafting of manuscript, manuscript revision, approval of final version, guarantor.
- All remaining authors of the High Risk of Preeclampsia Identification Group: study concept, manuscript revision, approval of final version

Funding

This work was supported by a Knowledge Synthesis grant from the Canadian Institutes for Health Research. Dr. Ray holds a Canadian Institutes for Health Research Chair in Reproductive and Child Health Services and Policy Research.

Data sharing

No additional data available.
Transparency

The lead authors (Bartsch and Ray) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Members of the High Risk of Preeclampsia Identification Group are, listed alphabetically:

Ziad TA Al-Rubaie, MBCHB, MPH
The University of Notre Dame Australia, Sydney, Australia
ziad.alrubaie1@my.nd.edu.au

Lisa M Askie, BN, MPH, PhD
NHMRC Clinical Trials Centre, University of Sydney, Australia
lisa.askie@ctc.usyd.edu.au

Emily Bartsch, BMSc
University of Toronto
emily.bartsch@mail.utoronto.ca

Howard Berger, MD
Head, Maternal Fetal Medicine and Obstetric Ultrasound
Department of Obstetrics and Gynecology, St. Michael's Hospital
bergerh@smh.ca

Jennifer Blake, MD MSc
Chief Executive Officer
Society of Obstetricians and Gynaecologists of Canada
Ottawa, Ontario
jblake@sogc.com

Lisa Graves, MD CCFP FCFP
Department of Family and Community Medicine
University of Toronto
Toronto, Ontario
lisa.graves@utoronto.ca

John C Kingdom, MD
Gordon C. Leitch Chair, Department of Obstetrics and Gynaecology
University of Toronto
Toronto, Ontario
jkingdom@mtsinai.on.ca

Gerald Lebovic, PhD
Applied Health Research Centre, St. Michael's Hospital
Toronto, Ontario
lebovicg@smh.ca
Sally J Lord, MBBS MSc
University of Notre Dame Australia, Australia
NHMRC Clinical Trials Centre, University of Sydney, Australia
Sally.Lord@ctc.usyd.edu.au

Jonathon L. Maguire, MD MSc
Departments of Paediatrics and Health Policy, Management and Evaluation,
St. Michael’s Hospital, University of Toronto
Toronto, Ontario
jonathon.maguire@utoronto.ca

Muhammad M Mamdani, PharmD, MPH
Li Ka Shing Knowledge Institute of St. Michael’s Hospital, University of Toronto
Toronto, Ontario
MamdaniM@smh.ca

Karyn Medcalf, BSc
University of Toronto
karyn.medcalf@mail.utoronto.ca

James Meloche
Executive Director
Provincial Council for Maternal and Child Health
Toronto, Ontario
james.meloche@pcmch.on.ca
Alison L Park, MSc
Institute for Clinical Evaluative Sciences
Toronto, Ontario
alison.park@ices.on.ca

Joel G Ray, MD MSc
Departments of Medicine, Health Policy Management and Evaluation,
and Obstetrics and Gynecology
St. Michael’s Hospital, University of Toronto
Toronto, Ontario
rayj@smh.ca

Marcelo L Urquia, PhD
Li Ka Shing Knowledge Institute of St. Michael’s Hospital
University of Toronto
Toronto, Ontario
urquiam@smh.ca

Vicki Van Wagner, RM PhD
Midwifery Education Program
Ryerson University
Toronto, Ontario
What this paper adds

What is already known

- Clinical practice guidelines strongly recommend that physicians and midwives start ASA at 12 to 16 weeks gestation in a woman at high risk of preeclampsia (PE).
- However, these guidelines do not provide a systematic approach for identifying a woman at high risk of PE, using readily available clinical risk factors (RFs) known before 16 weeks gestation.
- Thus, there is a need for a clear, concise and evidence-based list of RFs that clinicians can use, before 16 weeks gestation, to estimate a woman’s risk of PE.

What this study adds

- We systemically analyzed large cohort studies and generated three practical estimates.
- The first was the absolute pooled risk of developing PE in the presence vs. absence of one of 14 common RFs.
- The second was the pooled relative risk (RR) of developing PE in the presence vs. absence of one of 14 RFs.
- The third was the pooled population attributable fraction (PAF) for PE in relation to each RF.
- Antiphospholipid antibody syndrome, prior PE, chronic hypertension, pregestational diabetes, assisted reproductive technology and BMI > 30 kg/m² were most strongly associated with a high rate of PE, suggesting that the presence of any one might suffice to designate a woman as “high risk” for PE.
References


35 Blomberg M, Tyrberg RB, Kjolhede P. Impact of maternal age on obstetric and neonatal outcome with emphasis on primiparous adolescents and older women: A Swedish Medical Birth Register Study. BMJ Open 2014;4:e005840.


Figure 1. PRISMA flow diagram of the selection and inclusion of studies in the current meta-analysis.

Records identified through database searching
PubMed (n = 2567)
Embase, excluding duplicates from PubMed (n = 1481)

Titles and abstracts screened (n = 4048)

Publications that did not meet screening criteria (n = 3840)

Full-text articles retrieved and assessed for eligibility (n = 208)

Publications that did not meet inclusion criteria (n = 116)

Studies included in meta-analysis (n = 92)
Figure 2. Risk of preeclampsia among women with (dark grey bars) and without (light grey bars) individual clinical risk factors determined by 16 weeks gestation. Each bar shows the pooled rate (95% confidence interval) of preeclampsia. To the right of each pair of bars is the pooled unadjusted relative risk (RRp) for preeclampsia and its $I^2$ measure of heterogeneity. IUGR intrauterine growth restriction; SLE systemic lupus erythematosus; ART assisted reproductive technology; BMI body mass index; aPL antiphospholipid antibody syndrome; n/a not applicable.
Figure 3. Population attributable fraction for preeclampsia in relation to individual clinical risk factors determined by 16 weeks gestation. Each bar shows the population attributable fraction and 95% confidence interval. IUGR intrauterine growth restriction; SLE systemic lupus erythematosus; ART assisted reproductive technology; BMI body mass index; aPL antiphospholipid antibody syndrome.

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>(No. women in no. studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>2,413,908 women in 2 studies</td>
</tr>
<tr>
<td>aPL</td>
<td>220,156 women in 3 studies</td>
</tr>
<tr>
<td>PRIOR IUGR</td>
<td>55,542 women in 1 study</td>
</tr>
<tr>
<td>PRIOR PLACENTAL ABRUPTION</td>
<td>291,134 women in 3 studies</td>
</tr>
<tr>
<td>PRIOR STILLBIRTH</td>
<td>63,814 women in 2 studies</td>
</tr>
<tr>
<td>PREGESTATIONAL DIABETES</td>
<td>2,553,117 women in 19 studies</td>
</tr>
<tr>
<td>CHRONIC KIDNEY DISEASE</td>
<td>966,505 women in 5 studies</td>
</tr>
<tr>
<td>MATERNAL AGE &gt; 40 Y</td>
<td>4,260,202 women in 16 studies</td>
</tr>
<tr>
<td>MATERNAL AGE &gt; 35 Y</td>
<td>5,244,543 women in 22 studies</td>
</tr>
<tr>
<td>ART</td>
<td>1,463,529 women in 20 studies</td>
</tr>
<tr>
<td>MULTIFETAL PREGNANCY</td>
<td>7,309,227 women in 8 studies</td>
</tr>
<tr>
<td>CHRONIC HYPERTENSION</td>
<td>6,589,661 women in 20 studies</td>
</tr>
<tr>
<td>PRIOR PREECLAMPSIA</td>
<td>3,720,885 women in 20 studies</td>
</tr>
<tr>
<td>PRE-PREGNANCY BMI &gt; 30 KG/M2</td>
<td>5,921,599 women in 40 studies</td>
</tr>
<tr>
<td>PRE-PREGNANCY BMI &gt; 25 KG/M2</td>
<td>3,644,747 women in 38 studies</td>
</tr>
<tr>
<td>NULLIPARITY</td>
<td>2,975,158 women in 25 studies</td>
</tr>
</tbody>
</table>

Population attributable fraction (95% confidence interval)
Figure 4. Threshold number of women needed to receive ASA prophylaxis (NNP\textsubscript{T}) to prevent one case of preeclampsia, based on individual clinical risk factors determined by 16 weeks gestation. Each bar shows the NNP\textsubscript{T} and upper 95% confidence interval with a 10% (■, upper bar), 30% (●, middle bar) or 50% (□, bottom bar) reduction in the relative risk of preeclampsia with ASA prophylaxis. The red dashed line is the clinically important minimum NNP\textsubscript{T} of 250 women, based on reference 25. IUGR intrauterine growth restriction; SLE systemic lupus erythematosus; ART assisted reproductive technology; BMI body mass index; aPL antiphospholipid antibody syndrome.

**Risk Factor**

- aPL
  - 120,156 women in 3 studies
- Chronic Hypertension
  - 5,589,661 women in 20 studies
- Prior Preeclampsia
  - 3,720,885 women in 20 studies
- Pregestational Diabetes
  - 2,553,117 women in 19 studies
- Prior Placental Abruption
  - 291,134 women in 3 studies
- Multifetal Pregnancy
  - 7,309,227 women in 8 studies
- Pre-Pregnancy BMI > 30 kg/m\(^2\)
  - 5,921,559 women in 40 studies
- ART
  - 1,463,529 women in 20 studies
- Chronic Kidney Disease
  - 966,505 women in 5 studies
- Prior Stillbirth
  - 63,814 women in 2 studies
- Maternal Age > 40 y
  - 4,260,202 women in 16 studies
- Nulliparity
  - 2,975,158 women in 25 studies
- SLE
  - 2,413,908 women in 2 studies
- Prior IUGR
  - 55,542 women in 1 study

**Threshold number needed to prevent (NNP\textsubscript{T})**
Figure 5. A conceptual framework for identifying a woman at high risk of preeclampsia, in whom ASA would be recommended, based on individual clinical risk factors determined by 16 weeks gestation. ASA would be justified in a woman with a strong solitary risk factor (left circle), or two less prominent risk factors (right circle). BMI body mass index; IUGR intrauterine growth restriction.

ASA may be warranted if a woman has **one** of the following risk factors:

Antiphospholipid antibody syndrome  
Chronic hypertension  
Prior preeclampsia  
Pregestational diabetes  
Pre-pregnancy BMI > 30 kg/m²  
Assisted reproductive therapy

ASA may be warranted if woman has **two or more** of the following risk factors:

Prior placental abruption  
Multifetal pregnancy  
Chronic kidney disease  
Prior stillbirth  
Maternal age > 40 years  
Nulliparity  
Systemic lupus erythematosus  
Prior IUGR*

*There is a high level of uncertainty about the strength of the relation between prior IUGR and subsequent preeclampsia.
Supplemental file 4. Funnel plots for included cohort studies examining the relation between prior preeclampsia (panel A), chronic hypertension (panel B), or pre-pregnancy body mass index > 30 kg/m^2 (panel C), and the risk of preeclampsia in the index pregnancy.
Supplemental file 5. Pooled preeclampsia event rates among women in the current meta-analysis of large cohort studies (top, light grey bar), in contrast to the preeclampsia event rates in the placebo arm within a published meta-analysis of randomized clinical trials of ASA prophylaxis based on individual patient data\textsuperscript{13} (bottom, dark grey bar). Shown are those preeclampsia risk factors available in both of types of meta-analyses.

*The current meta-analysis of large cohort studies only examined prior preeclampsia, while the previously published meta-analysis of randomized clinical trials of ASA prophylaxis considered prior hypertensive disorders of pregnancy (i.e., prior gestational hypertension or preeclampsia).\textsuperscript{13}