First trimester serum matrix metalloproteinase-7 is a poor predictor of late-onset preeclampsia

Ravn, Julie Dahl; Bendix, Emma Julie; Sperling, Lene; Overgaard, Martin

Published in:
Pregnancy Hypertension

DOI:
10.1016/j.preghy.2022.03.002

Publication date:
2022

Document version:
Final published version

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 28 (2022) 94–99

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

First trimester serum matrix metalloproteinase-7 is a poor predictor of late-onset preeclampsia

Julie Dahl Ravn [a], Emma Julie Bendix [a], Lene Sperling [a,b], Martin Overgaard [b,c,*,1]

[a] Department of Obstetrics and Gynecology, Odense University Hospital, Odense, Denmark
[b] Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[c] Department of Clinical Biochemistry, Odense University Hospital, Odense, Denmark

ARTICLE INFO

Keywords:
Pre-eclampsia
Pregnancy-induced hypertension
Maternal serum screening tests
Matrix metalloproteinase 7
Uterine artery

ABSTRACT

Objectives: This study aims to evaluate matrix metalloproteinase-7 as a first trimester biomarker for late-onset preeclampsia, both alone and in combination with mean arterial pressure, uterine artery pulsatility index, and maternal characteristics.
Study design: We conducted a nested case-control study from a prospective cohort consisting of 416 pregnant women who attended a routine first trimester scan. Baseline variables were obtained at inclusion and analysed subsequently to formation of case and control groups. The study was designed to detect a mean difference of > 15% in matrix metalloproteinase-7 concentrations between groups with a statistical power of 80%.
Main outcome measures: The primary outcome was preeclampsia with delivery after 34 weeks of pregnancy.
Results: The median matrix metalloproteinase-7 concentration in cases of late-onset preeclampsia (n = 27) was marginally lower compared to normotensive controls but this difference was not statistically significant. Matrix metalloproteinase-7 predicted 14.8% of cases at a 10% false-positive rate. Addition of matrix metalloproteinase-7 to any combination of variables did not significantly improve their performance.
Conclusions: Matrix metalloproteinase-7 is not a useful biomarker for late-onset preeclampsia, neither alone nor in combination with mean arterial pressure, uterine artery pulsatility index, or maternal characteristics.

1. Introduction

Preeclampsia (PE) is a multi-organ hypertensive disorder of pregnancy. An estimated 3–8% of pregnancies are affected, making the condition one of the leading causes of pregnancy-related complication and mortality worldwide [1]. Additionally, multiple studies have shown a clear association between PE and long-term cardiovascular risk, most likely due to shared pre-pregnancy risk factors [2,3].

Preeclampsia is a heterogeneous disease, the epidemiology, clinical presentation, and associated morbidity of which depends especially on timing of onset. Consequently, a distinction between early-onset PE (EO-PE) and late-onset PE (LO-PE) is made, typically at 34 weeks of gestation at delivery [4]. Due to the higher gestational age (GA), neonatal mortality is significantly lower in cases of LO-PE, which in turn accounts for 75–90% of cases and appears to be proportionally more frequent in high-income countries [4–7]. Despite occasionally labelled 'mild PE', LO-PE is a real source of severe morbidity and should, as any case of PE, be considered potentially threatening [8]. Most study evidence supports that PE is associated with a combination of placental and endothelial dysfunction, but whether it constitutes a disease spectrum or a syndrome with several distinct etiologies remains up for debate [9,10].

As the only known cure for PE is delivery of the placenta [4,10], considerable effort has gone into researching prediction and prevention of the disease. The first trimester Fetal Medicine Foundation (FMF) algorithm combines maternal characteristics, mean arterial pressure (MAP), and uterine artery pulsatility index (UtA PI) with serum markers pregnancy-associated plasma protein A and placental growth factor – a method which has shown to predict 90% of EO-PE and 75% of preterm

Abbreviations: PE, preeclampsia; EO-PE, early-onset preeclampsia; LO-PE, late-onset preeclampsia; GA, gestational age; FMF, Fetal Medicine Foundation; MAP, mean arterial pressure; UtA PI, uterine artery pulsatility index; MMP, matrix metalloproteinase; ISSHP, International Society for the Study of Hypertension in Pregnancy; BMI, body mass index; ROC, receiver operating characteristic.

* Corresponding author at: Department of Clinical Biochemistry, Odense University Hospital, J.B. Winsløws Vej 4, 5000 Odense C, Denmark.
E-mail addresses: juliedahlravn@gmail.com (J.D. Ravn), Martin.Overgaard@rsyd.dk (M. Overgaard).
[1] ORCID: 0000-0003-2277-590X.

https://doi.org/10.1016/j.preghy.2022.03.002
Received 14 September 2021; Received in revised form 28 February 2022; Accepted 10 March 2022
Available online 12 March 2022

PE (delivery < 37 weeks) cases [11]. In a randomised controlled trial, early administration of low-dose aspirin to participants assessed as high risk according to the FMF algorithm lowered PE incidence by 90% for EO-PE and 60% for preterm PE [12]. However, the FMF algorithm has not proven effective in cases of LO-PE and especially term PE (delivery > 37 weeks), and the effectiveness of aspirin for the prevention of LO-PE remains to be established [11–14]. What we have learned is that maternal characteristics, MAP, and UtA PI can predict some term-PE cases, while the two serum markers, pregnancy-associated plasma protein A and placental growth factor, do not appear to contribute to the prediction of LO-PE at all [11].

Matrix metalloproteinases (MMPs) have recently become a target of interest in relation to the pathophysiology of PE due to their implication in vascular remodeling, angiogenesis, and both uterine and systemic vasodilation during normal pregnancy [15]. The smallest of the MMPs, MMP-7 (called matrilysin), degrades components of extracellular matrix such as collagen, elastin, and proteoglycan [16]. In the first trimester, MMP-7 is expressed in the decidua and trophoblast as well as uterine NK cells and macrophages and is required for growth and remodelling of uterus and placenta [15–17]. In placentas of patients with severe pre-eclampsia, there is extensive immunostaining for MMP-7 in all layers of villous trophoblast as compared to uncomplicated pregnancies [17]. Thus, dysregulation of this proteolytic enzyme could play a role in the pathogenesis leading to PE. In a proteomics-based study, MMP-7 was shown to be the single best predictor of LO-PE in the first and second trimester [18]. This result, however, remains to be validated in a different pregnancy cohort.

In the present study, we hypothesise that MMP-7 is an early predictor of LO-PE and that it can improve screening for the disorder, either alone or when combined with MAP, UtA PI, or maternal characteristics.

2. Methods

2.1. Study design and participants

This study is a nested case-control study from a prospective cohort. The cohort consists of 416 pregnant women who attended a routine first trimester scan at Odense University Hospital in the time period 13 August 2019–18 November 2019, fulfilled the inclusion criteria (Fig. 1), and consented to participate. The primary outcome was LO-PE and the case group consists of all participants who developed LO-PE in their pregnancies. The control group consists of 194 participants who were unaffected by hypertension in pregnancy (Fig. 1).

2.2. Procedures

We determined GA by ultrasound measurement of fetal crown-rump length. First trimester prenatal risk assessment, and thus participation in the study, required a crown-rump length of between 45 and 84 mm. Blood pressure was recorded with the participant seated and arms elevated to the level of the heart, cuffs placed simultaneously around both arms. After a resting period of five minutes, three sets of measurements were recorded. Maternal characteristics and medical history were obtained from self-reported data and verbally confirmed by participants at the time of inclusion. Right and left UtA PI were recorded by transabdominal colour Doppler ultrasound using the Voluson E10 ultrasound system (GE Healthcare). The sonographers who performed these scans were FMF certified and had received relevant training in doing so. We sampled venous blood from all participants. These procedures were carried out in any order convenient for participants and staff.

All participants received written and oral information about the study and provided their written consent for participation. No health risks were associated with participation in the study. Uterine artery pulsatility index values recorded for the purpose of the study were not made known to participants and did not influence subsequent management. Instances of recorded hypertension were treated according to Danish obstetric guidelines.

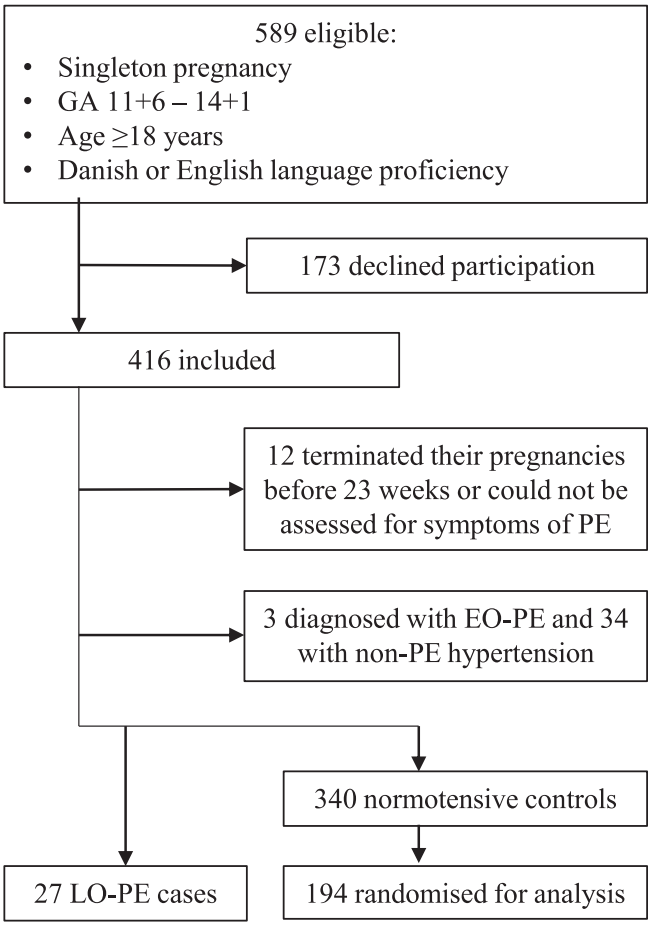

Fig. 1. Flowchart of eligibility criteria, enrolment, outcome, and randomisation.
Abbreviations: GA = gestational age, PE = preeclampsia, EO-PE = early-onset preeclampsia, LO-PE = late-onset preeclampsia.

2.3. Classification of outcome

We collected outcome data from electronic health records no more than 14 days after participants had given birth or terminated their pregnancies. Several project staff independently reviewed the medical records of participants who experienced hypertension in pregnancy. A fetal medicine specialist reviewed all fetal growth restriction diagnoses.

Preeclampsia was diagnosed according to International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines [8]. All cases of PE with delivery after 34 weeks of gestation were classified as LO-PE.

2.4. Biochemical analyses

Blood samples coagulated for at least 30 min prior to centrifugation. All samples were centrifuged within 8 h and stored at 2–8° C, then aliquoted and frozen at −80° C within 24 h of sampling. We analysed serum samples batch-wise for MMP-7 using a Human Total MMP-7 Quantikine ELISA Kit (R&D Systems). The assay was performed according to manufacturer instructions using an automated immunoassay system (Tritius ELISA analyser). Analysis of serum quality control samples yielded a mean intra-assay coefficient of variation for MMP-7 at 2.1 ng/mL of 18.0% (10.6%–24.1%). The inter-assay coefficient of variation at the same concentration was 20.4%.

2.5. Statistical analyses

We expected serum samples to show at least a 15% difference in expression levels between groups. With an expected standard deviation of 25%, a statistical power of 80% (1-β = 0.80) and a risk of type 1 error of 5% (α = 0.05) at 95% confidence interval, we calculated a necessary sample size of 26 cases and 156 controls.

Blood pressure was processed as MAP, which is superior to systolic or diastolic blood pressure in predicting PE [19]. Gestational age, maternal age, MAP, UtA PI, body mass index (BMI), and serum MMP-7 levels were treated as continuous variables. Parity and PE in a previous pregnancy were treated as categorical variables. Smoking, method of conception, and family history of PE were treated as binary variables.

For univariate statistical comparison, we used the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical and binary variables. Univariate and multivariate prediction models were generated using logistic regression and receiver operating characteristic (ROC) curves were generated for the assessment of discrimination. 95% confidence intervals for detection rates and ROC curves were generated using percentiles from 1000 bootstraps.

False positive rate is equal to 1-specificity and detection rate is synonymous with sensitivity. A significance level of $P < 0.05$ was applied for all statistical tests in this study. We used Stata IC 16.0 statistical software (StataCorp LCC) for our analyses. Missing data were handled by listwise deletion.

Ethical approval

This study was performed in accordance with the Helsinki Declaration II, approved by the Committee on Health Ethics (Videnskabsetisk Komité) of Region Hovedstaden (project ID H-19001203S), and reported to the Danish Data Protection Agency (Fortegnelsen; j.no. 20/27216).

3. Results

Three participants in the cohort developed EO-PE and 27 developed LO-PE. Of the 404 who were pregnant beyond 23 weeks and could be assessed for symptoms of PE, this is equivalent to a total PE incidence of 7.4% and a relative LO-PE incidence of 90%. Baseline characteristics of case and control groups are summarised and compared in Table 1. Compared to the normotensive group, participants in the case group had a higher BMI ($P < 0.001$), were more frequently nulliparous ($P = 0.003$), had a higher first trimester MAP ($P < 0.001$), and were less likely to have conceived spontaneously ($P = 0.032$). Median serum MMP-7 levels were 8.7% lower in the case group, but this difference was not statistically significant ($P = 0.401$). Odds ratios of baseline variables are detailed in Supplementary Material, Table S1.

Neither MMP-7 nor UtA PI showed any significant discriminatory capacity as single variables and when combined with any other variables MMP-7 failed to improve their performance (Table 2 and Fig. 2). While MAP performed significantly better than both UtA PI and MMP-7 as single variables, it is worth noting that no combination of variables was significantly superior to another.

Comparing our cohort to the non-participating target population in the same time period, there were no significant differences in age, GA at baseline, frequency of assisted conception, or frequency of smoking. Those who participated did, however, have higher BMI, lower parity, and were less frequently of African or Asian descent.

Table 1
Baseline characteristics of case and control groups.

	Controls (n = 194)	Cases (n = 27)	P-value
GA in weeks + days, median (IQR)	12 + 4 (12 + 2–12 + 6)	12 + 5 (12 + 2–12 + 7)	0.269
Age in years, median (IQR)	29 (26–32)	30 (27–33)	0.200
BMI in kg/m2, median (IQR)	23.6 (21.9–28.0)	27.7 (25.1–34.9)	<0.001
Ethnicity*			
white, n (%)	192 (99%)	26 (96%)	0.325
Method of conception			
assisted, n (%)	7 (4%)	4 (15%)	0.032
Smoking in pregnancy, n (%)	11 (6%)	1 (4%)	1.000
Participant's birth mother had PE, n (%)	6 (3%)	2 (7%)	0.254
Medical history			
essential hypertension, n (%)	0	1 (4%)	0.122
Obstetric history			
nulliparous, n (%)	77 (40%)	19 (70%)	0.003
multiparous with previous PE, n (%)	82 (42%)	21 (78%)	0.064
Prophylactic aspirin treatment**	0	3	0.002
MAP in mmHg, median (IQR)	78.39 (75–84.3)	89.1 (81.17–92.78)	<0.001
UtA PI, median (IQR)***	1.5 (1.27–1.85)	1.39 (1.15–2.02)	0.661
MMP-7 in ng/mL, median (IQR)	2.31 (1.83–2.85)	2.11 (1.81–2.80)	0.401

This table lists the baseline characteristics of the case and control groups together with the statistical level of significance of any difference between the two groups.
*two participants did not have their ethnicity listed.
**prophylactic aspirin treatment refers to the treatment with 150 mg acetylsalicylic acid daily started before 16 weeks of gestation.
***18 participants did not have their UtA PI measured and two had only a unilateral measurement.
Abbreviations: GA = gestational age, IQR = interquartile range, BMI = body mass index, PE = preeclampsia, MAP = mean arterial pressure, UtA PI = uterine artery pulsatility index, MMP-7 = matrix metalloproteinase-7.

Table 2
Performance of screening for late-onset preeclampsia.

	Sensitivity at 10% FPR (%)	95% CI (%)	AUROC	95% CI
MMP-7	14.8	3.6–30.0	0.548	0.442–0.662
Maternal characteristics*	51.9	32.1–71.9	0.829	0.746–0.902
Maternal characteristics + MMP-7**	51.9	30.9–71.9	0.831	0.752–0.909
MAP	44.4	21.3–66.7	0.803	0.722–0.877
MAP + MMP-7	44.4	17.9–66.7	0.815	0.734–0.884
UtA PI***	13.6	4.0–33.3	0.528	0.382–0.677
UtA PI + MMP-7***	13.6	3.8–29.4	0.560	0.441–0.683

This table lists the sensitivity at 10% FPR together with the AUROC of screening models for late-onset preeclampsia by combinations of different variables.
*Maternal characteristics include the variables maternal age, parity, and BMI.
**These multivariate models are likely to be overfitted due to the number of variables.
***18 participants did not have their uterine artery pulsatility index measured, and two had only a unilateral measurement.
Abbreviations: FPR = false-positive rate, CI = confidence interval, AUROC = area under receiver operating characteristics, BMI = body mass index, MAP = mean arterial pressure, UtA PI = uterine artery pulsatility index, MMP-7 = matrix metalloproteinase-7.

4. Discussion

This study shows that MMP-7 measured between 11 and 14 weeks of pregnancy can predict 14.8% of LO-PE cases at a 10% FPR. In comparison, a previous study by Erez et al. [18] showed that MMP-7 measured between 8 and 16 weeks of pregnancy could predict 57% of LO-PE cases at the same FPR. Several factors may explain this difference. Firstly, the participants in the study by Erez et al. were mainly African American, placing them at much higher risk of LO-PE than our almost exclusively white study sample [20]. Secondly, the GA range at which blood was sampled was broader in the Erez et al. study, including both earlier and later sampling. Thirdly, it is unknown to what extent the aptamer-based

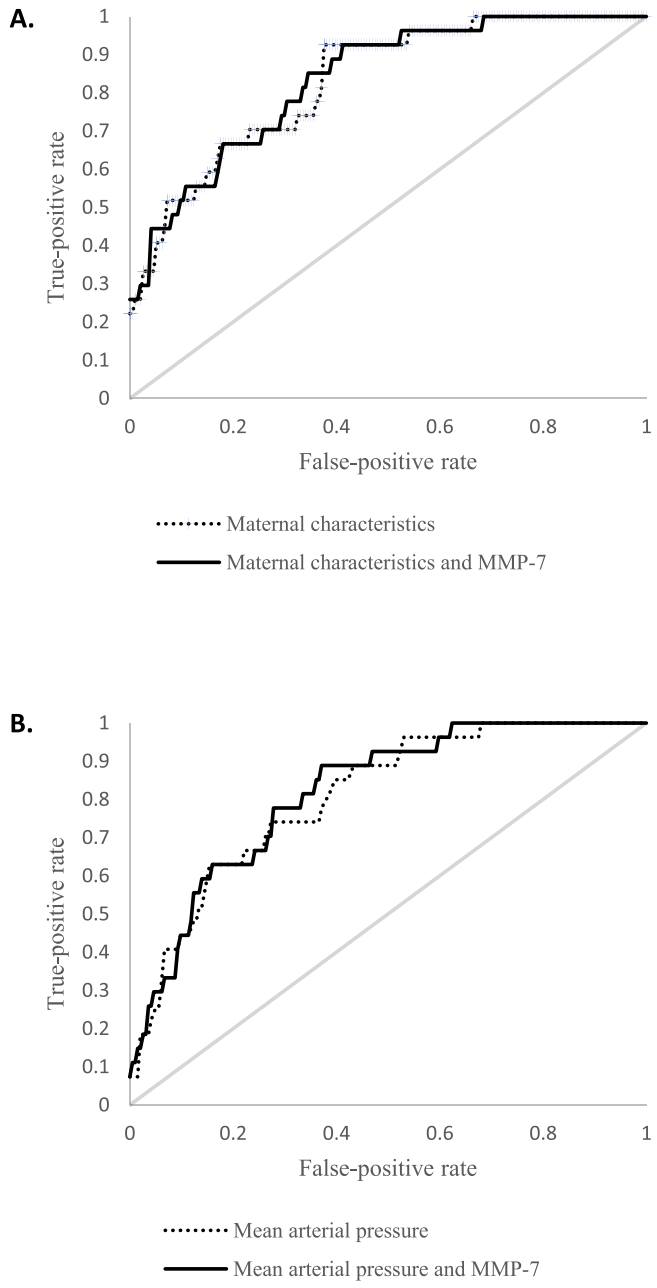

Fig. 2. Receiver operating characteristic curve for the prediction of LO-PE **A.** by maternal characteristics alone and combined with MMP-7 **B.** by MAP alone and combined with MMP-7.
Abbreviations: LO-PE = late-onset preeclampsia, MMP-7 = matrix metalloproteinase-7, MAP = mean arterial pressure, ROC = receiver operating characteristic.

MMP-7 method used by Erez et al. compare to the commercial ELISA test used in this study. The study designs, comparing the case group to a group of unaffected controls, are similar in both studies. All these factors considered, our study falls short of providing evidence that MMP-7 is a useful screening marker for LO-PE in our study population, instead underlining the importance of thorough validation of omics-based biomarker data.

The incidence of PE in our cohort is 7.4%. Recent reports from Swedish, Danish and Dutch populations find incidence rates ranging from 2.8% to 8.2% [21–23]. These variations may be explained by the use of different diagnostic criteria and study designs. For instance, a 2019 study describes a large Danish cohort with a PE incidence of 3.9%, but only after the exclusion of participants with any of several risk factors for PE, including chronic hypertension, pre-gestational or gestational diabetes mellitus, and metabolic disorders. A Dutch cohort published in 2020 using a very similar study design and the same diagnostic criteria as our study reports a PE incidence of 8.2% [21].

In this study, the combination of maternal age, parity, and BMI achieved a 51.9% detection rate at a 10% FPR. In comparison, previous research has found first trimester models predicting between 64.2% and 76.5% of LO-PE cases at the same FPR [24–26]. However, these studies all reference the 2001 ISSHP guidelines, diagnosing PE only when proteinuria is present [27]. Since a 2014 ISSHP statement introduced much broader diagnostic criteria for PE [28], it is likely that the accuracy of these prediction models would be relatively lower if applied to the now more heterogeneous definition of PE.

Currently, there is no commonly accepted LO-PE prophylaxis and thus screening for the condition is not critically time-sensitive. Rather, second/third trimester or longitudinal screening could prove useful, if possible, for determining appropriate time of delivery and avoiding unnecessary iatrogenic preterm delivery. Indeed, recent research has found second and third trimester biomarkers with detection rates of 75% for LO-PE and 82% for term PE at a 10% FPR [29,30]. On the other hand, combined first trimester screening for chromosome abnormalities, EO-PE, and LO-PE could provide advantages such as convenient scheduling of antenatal care and personalised monitoring throughout pregnancy.

4.1. Strengths and limitations

This study is based on a prospective cohort of pregnant women attending the Danish first trimester screening programme, which has a participation rate of > 90% [31]. Seventy per cent of the eligible target population enrolled. Because the Danish healthcare system is highly centralised, there was no loss of data to follow-up in the cohort. These factors increase representativeness of the study sample.

It is necessary to consider that the control group in this study consists of participants who were entirely unaffected by hypertension in pregnancy. It has previously been shown that some maternal factors and biomarkers predictive of PE are also predictive of non-PE gestational hypertension to a varying degree [20,32,33]. Hence, by using unaffected controls, we wanted to ensure any difference between cases and controls not be initially overlooked. However, this also means that our prediction model would most likely yield a lower accuracy if used in a real-life clinical setting.

This study is limited by the degree of precision of our MMP-7 analyses, of which intra and inter assay coefficients of variation were all >15%. Because the biological variation adds to the analytical variation, real differences in MMP-7 serum concentration between groups may have been too small to detect with statistical significance.

The objective of this study is not to assess the FMF algorithm nor any of its individual variables and its design may be under-powered for this purpose. Considering the number of cases available, some combined models presented, especially those containing more than four variables, are at risk of being overfitted. Furthermore, there were not enough events per non-white ethnicity or any pre-existing medical conditions for these variables to be assessed for discrimination at all. It is thus likely that our prediction models would have performed better had the case group been large enough to allow for a more complex regression model and/or had more variables been available for evaluation.

5. Conclusions

First trimester serum MMP-7 is a poor predictor of LO-PE in our study population. When combined with either UtA PI, MAP, or maternal characteristics, MMP-7 did not significantly improve their predictive performance.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This research project was conducted with the support of OPEN, Open Patient data Explorative Network, Odense University Hospital, Region of Southern Denmark, namely OPEN Biobank and OPEN Statistics. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Region Syddanmark. We thank the sonographers at the Department of Obstetrics and Gynecology for performing all uterine artery Doppler measurements for this study, and Christian Enggaard and Niels Strømvig Larsen at the Department of Clinical Biochemistry for excellent technical laboratory assistance.

Funding details

This work was supported by the OUH Free Research Fund (72-A3727), which had no involvement in its conduction or subsequent publication.

Contributors

Julie Dahl Ravn: I declare that I participated in data collection, data analysis, and writing of this article and that I have seen and approved the final version. I have the following conflicts of interest: none.

Emma Julie Bendix: I declare that I participated in data collection for this article and that I have seen and approved the final version. I have the following conflicts of interest: none.

Lene Sperling: I declare that I participated in designing this study and oversaw its supervision and that I have seen and approved the final version. I have the following conflicts of interest: none.

Martin Overgaard: I declare that I participated in designing this study, application for funding, supervision, and participated in data analysis for this article and that I have seen and approved the final version. I have the following conflicts of interest: none.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2022.03.002.

References

[1] E. Abalos, C. Cuesta, A.L. Grosso, D. Chou, L. Say, Global and regional estimates of preeclampsia and eclampsia: a systematic review, Eur. J. Obstet. Gynecol. Reprod. Biol. 170 (1) (2013) 1–7.

[2] P. Wu, R. Haththotuwa, C.S. Kwok, A. Babu, R.A. Kotronias, C. Rushton, A. Zaman, A.A. Fryer, U. Kadam, C.A. Chew-Graham, M.A. Mamas, Preeclampsia and future cardiovascular health: A systematic review and meta-analysis, Circ. Cardiovasc. Qual. Outcomes 10 (2) (2017).

[3] P.R. Romundstad, E.B. Magnussen, G.D. Smith, L.J. Vatten, Hypertension in pregnancy and later cardiovascular risk: common antecedents? Circulation 122 (6) (2010) 579–584.

[4] L.C. Poon, A. Shennan, J.A. Hyett, A. Kapur, E. Hadar, H. Divakar, F. McAuliffe, F. da Silva Costa, P. von Dadelszen, H.D. McIntyre, A.B. Kihara, G.C. Di Renzo, R. Romero, M. D'Alton, V. Berghella, K.H. Nicolaides, M. Hod, The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention, Int. J. Gynaecol. Obstet. 145 (Suppl 1) (2019) 1–33.

[5] S. Lisonkova, Y. Sabr, C. Mayer, C. Young, A. Skoll, K.S. Joseph, Maternal morbidity associated with early-onset and late-onset preeclampsia, Obstet. Gynecol. 124 (4) (2014) 771–781.

[6] L.C. Poon, K.H. Nicolaides, Early prediction of preeclampsia, Obstet Gynecol Int 2014 (2014), 297397.

[7] P.Y. Robillard, G. Dekker, G. Chaouat, M.G. Elliot, M. Scioscia, High incidence of early onset preeclampsia is probably the rule and not the exception worldwide. 20th anniversary of the reunion workshop. A summary, J. Reprod. Immunol. 133 (2019) 30–36.

[8] M.A. Brown, L.A. Magee, L.C. Kenny, S.A. Karumanchi, F.P. McCarthy, S. Saito, D. R. Hall, C.E. Warren, G. Adoyi, S. Ishaku, P., International Society for the Study of Hypertension in, Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice, Hypertension 72 (1) (2018) 24–43.

[9] G.J. Burton, C.W. Redman, J.M. Roberts, A. Moffett, Pre-eclampsia: pathophysiology and clinical implications, BMJ 366 (2019), l2381.

[10] A.C. Staff, The two-stage placental model of preeclampsia: An update, J. Reprod. Immunol. 134–135 (2019) 1–10.

[11] M.Y. Tan, A. Syngelaki, L.C. Poon, D.L. Rolnik, N. O'Gorman, J.L. Delgado, R. Akolekar, L. Konstantinidou, M. Tsavdaridou, S. Galeva, U. Ajdacka, F.S. Molina, N. Persico, J.C. Jani, W. Plasencia, E. Greco, G. Papaioannou, A. Wright, D. Wright, K.H. Nicolaides, Screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation, Ultrasound Obstet. Gynecol. 52 (2) (2018) 186–195.

[12] D.L. Rolnik, D. Wright, L.C. Poon, N. O'Gorman, A. Syngelaki, C. de Paco Matallana, R. Akolekar, S. Cicero, D. Janga, M. Singh, F.S. Molina, N. Persico, J. C. Jani, W. Plasencia, G. Papaioannou, K. Tenenbaum-Gavish, H. Meiri, S. Gizurarson, K. Maclagan, K.H. Nicolaides, Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia, N. Engl. J. Med. 377 (7) (2017) 613–622.

[13] P.G. Lan, A.G. Gillin, M. Pelosi, J. Tooher, P. Sandager, J. Hyett, Effect of early use of low-dose aspirin therapy on late-onset preeclampsia, J. Matern. Fetal Neonatal. Med. 32 (13) (2019) 2137–2142.

[14] G.S. Moore, A.A. Allshouse, A.L. Post, H.L. Galan, K.D. Heyborne, Early initiation of low-dose aspirin for reduction in preeclampsia risk in high-risk women: a secondary analysis of the MFMU High-Risk Aspirin Study, J. Perinatol. 35 (5) (2015) 328–331.

[15] S. Espino Y. Sosa, A. Flores-Pliego, A. Espejel-Nuñez, D. Medina-Bastidas, F. Vadillo-Ortega, V. Zaga-Clavellina, G. Estrada-Gutierrez, New insights into the role of matrix metalloproteinases in preeclampsia, Int. J. Mol. Sci. 18 (7) (2017) 1448.

[16] B. Burke, The role of matrix metalloproteinase 7 in innate immunity, Immunobiology 209 (1–2) (2004) 51–56.

[17] I.M. Vettraino, J. Roby, T. Tolley, W.C. Parks, Collagenase-I, stromelysin-I, and matrilysin are expressed within the placenta during multiple stages of human pregnancy, Placenta 17 (8) (1996) 557–563.

[18] O. Erez, R. Romero, E. Maymon, P. Chaemsaithong, B. Done, P. Pacora, B. Panaitescu, T. Chaiworapongsa, S.S. Hassan, A.L. Tarca, The prediction of late-onset preeclampsia: Results from a longitudinal proteomics study, PLoS One 12 (7) (2017) e0181468.

[19] J.S. Cnossen, K.C. Vollebregt, N. de Vrieze, G. ter Riet, B.W. Mol, A. Franx, K. S. Khan, J.A. van der Post, Accuracy of mean arterial pressure and blood pressure measurements in predicting pre-eclampsia: systematic review and meta-analysis, BMJ 336 (7653) (2008) 1117–1120.

[20] L.C. Poon, N.A. Kametas, T. Chelemen, A. Leal, K.H. Nicolaides, Maternal risk factors for hypertensive disorders in pregnancy: a multivariate approach, J. Hum. Hypertens. 24 (2) (2010) 104–110.

[21] A.R. Bouter, J.J. Duvekot, Evaluation of the clinical impact of the revised ISSHP and ACOG definitions on preeclampsia, Pregnancy Hypertens 19 (2020) 206–211.

[22] C. Rohr Thomsen, T. Brink Henriksen, N. Uldbjerg, I. Milidou, Seasonal variation in the hypertensive disorders of pregnancy in Denmark, Acta Obstet. Gynecol. Scand. 99 (5) (2020) 623–630.

[23] Y. Yang, I. Le Ray, J. Zhu, J. Zhang, J. Hua, M. Reilly, Preeclampsia prevalence, risk factors, and pregnancy outcomes in Sweden and China, JAMA Netw. Open 4 (5) (2021).

[24] R. Akolekar, A. Syngelaki, R. Sarquis, M. Zvanca, K.H. Nicolaides, Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11–13 weeks, Prenat. Diagn. 31 (1) (2011) 66–74.

[25] F. Crovetto, F. Figueras, F. Crispi, S. Triunfo, M. Pugia, L. Lasalvia, A.E. Chambers, W.E. Mills, S. Banerjee, I. Mercade, E. Casals, A. Mira, L. Rodriguez-Revenga Bodi, E. Gratacos, Forms of circulating luteinizing hormone human chorionic gonadotropin receptor for the prediction of early and late preeclampsia in the first trimester of pregnancy, Fetal Diagn. Ther. 38 (2) (2015) 94–102.

[26] F. Crovetto, F. Figueras, S. Triunfo, F. Crispi, V. Rodriguez-Sureda, C. Dominguez, E. Llurba, E. Gratacos, First trimester screening for early and late preeclampsia based on maternal characteristics, biophysical parameters, and angiogenic factors, Prenat. Diagn. 35 (2) (2015) 183–191.

[27] M.A. Brown, M.D. Lindheimer, M. de Swiet, A.V. Assche, J.-M. Moutquin, The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP), Hypertens Pregnancy 20 (1) (2001) ix–xiv.

[28] A.L. Tranquilli, G. Dekker, L. Magee, J. Roberts, B.M. Sibai, W. Steyn, G.G. Zeeman, M.A. Brown, The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP, Pregn. Hypertens. 4 (2) (2014) 97–104.

[29] S. Andrietti, M. Silva, A. Wright, D. Wright, K.H. Nicolaides, Competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 35–37 weeks' gestation, Ultrasound Obstet. Gynecol. 48 (1) (2016) 72–79.

[30] C. Hirashima, T. Ohmaru-Nakanishi, S. Nagayama, K. Takahashi, H. Suzuki, H. Takahashi, R. Usui, K. Shirasuna, S. Matsubara, A. Ohkuchi, Serum soluble LIGHT in the early third trimester as a novel biomarker for predicting late-onset preeclampsia, Pregn. Hypertens 14 (2018) 174–176.

[31] C.K. Ekelund, O.B. Petersen, F.S. Jorgensen, S. Kjaergaard, T. Larsen, A.W. Olesen, L. Skibsted, P. Skovbo, S. Sommer, L. Sperling, B. Stavnstrup, B. Storup, H. Zingenberg, N. Uldbjerg, C.B. Miltoft, L. Noergaard, C.B. Wulff, A. Tabor, G., Danish Fetal Medicine Research, The Danish Fetal Medicine Database: establishment, organization and quality assessment of the first trimester screening

program for trisomy 21 in Denmark 2008–2012, Acta Obstet. Gynecol. Scand. 94 (6) (2015) 577–583.

[32] W. Plasencia, N. Maiz, S. Bonino, C. Kaihura, K.H. Nicolaides, Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia, Ultrasound Obstet. Gynecol. 30 (5) (2007) 742–749.

[33] L.C. Poon, N.A. Kametas, I. Pandeva, C. Valencia, K.H. Nicolaides, Mean arterial pressure at 11(+0) to 13(+6) weeks in the prediction of preeclampsia, Hypertension 51 (4) (2008) 1027–1033.