Preeclampsia prediction model using the dipstick test for proteinuria during early gestation

Hisashi Ohseto

Tohoku University Hospital

Mami Ishikuro (✉ m_ishikuro@med.tohoku.ac.jp)

Tohoku Medical Megabank Organization

Taku Obara

Tohoku Medical Megabank Organization

Keiko Murakami

Tohoku Medical Megabank Organization

Tomomi Onuma

Tohoku Medical Megabank Organization

Aoi Noda

Tohoku Medical Megabank Organization

Fumihiko Ueno

Tohoku Medical Megabank Organization

Noriyuki Iwama

Tohoku University Hospital

Masahiro Kikuya

Teikyo University School of Medicine

Hirohito Metoki

Tohoku Medical and Pharmaceutical University

Junichi Sugawara

Tohoku University Hospital

Shinichi Kuriyama

Tohoku Medical Megabank Organization

Research Article

Keywords: competing risk model, hypertensive disorders of pregnancy, prediction model, preeclampsia, proteinuria, The Tohoku Medical Megabank

Posted Date: September 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-887730/v1>

Abstract

Objective

The aim of our study was to develop prediction model for preeclampsia (PE) using routinely examined items in early pregnancy especially dipstick test for proteinuria.

Method

The Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study recruited pregnant women and we included 9,086 of them in analysis. Maternal basic characteristics were obtained by self-report, and blood pressure and dipstick test of proteinuria were obtained by medical record at regular antenatal care. The outcome was defined as PE including superimposed preeclampsia. We developed prediction model without dipstick test of proteinuria (model 1) and model with it (model 2), and we compared them by the mean of area under the receiver operating characteristic curve (mAUC) using five-fold cross validation.

Results

mAUC of model 1 was 0.769 (95% CI; 0.741 to 0.797) and that of model 2 was 0.785 (95% CI; 0.758 to 0.812). The difference of two mAUCs was 0.016 (95% CI; 0.004 to 0.028). In model 2, detection rates at false-positive rate of 5%, 10% and 20% were 40%, 49% and 64%, respectively.

Conclusions

We could develop prediction model for PE using routine antenatal care items and it was improved by including dipstick test for proteinuria.

Introduction

Preeclampsia (PE) affects about 3.4% of all pregnant women¹ and is one of the major causes of maternal and fetal morbidity.^{2,3} In addition, women with PE are at increased risk of future cardiovascular diseases.⁴ Previous studies have suggested that early intervention in high-risk pregnant women was effective in preventing PE,⁵⁻⁷ and several prevention methods for PE, such as daily aspirin, calcium, and L-arginine supplementation, have been reported. However, considering the possible adverse effects or economic burdens of PE, the prediction of women at high-risk for PE is critical for prompt and effective prevention.

A number of studies have developed prediction models for PE, using maternal characteristics combined with several biomarkers,⁸ such as uterine artery doppler,^{9,10} placental growth factor (PLGF),¹⁰ and maternal serum pregnancy-associated plasma protein-A (PAPP-A).^{10,11} While these biomarkers improved the prediction of PE, screening methods using these biomarkers do not prevail in clinical practice, partly

due to cost-effectiveness and technical difficulty. From this perspective, a prediction model for PE using only clinically common variables, such as blood pressure and proteinuria, is needed.

Although the pathogenesis of PE is not well understood, the two-stage model of pathogenesis is currently accepted as the standard theory. According to this theory, in the first stage, placental ischemia results from incomplete spiral artery remodeling and, in second stage, the placenta releases antiangiogenic factors to maternal circulation¹². These antiangiogenic factors cause systematic endothelial damage resulting in proteinuria, pulmonary edema, and eclampsia¹². Proteinuria is one of the criteria for diagnosis of PE, in addition to de-novo hypertension present after 20 weeks of gestation^{13,14}, and may result from the dysfunction of multiple organs, including the kidneys¹⁵; thus, proteinuria can be a good biomarker to indicate the clinical course of PE. Dipstick tests are popular as screening for proteinuria at prenatal care centers in Japan instead of 24h urine collection, and the World Health Organization recommended that proteinuria should be measured at every antenatal care visit¹⁶. A prediction model that includes the dipstick test for proteinuria as a predictor variable can be easily applied in clinical practice, although no studies to date have included it in their prediction model as a predictor variable.

The aim of our study was to develop a prediction model for PE using items routinely examined in early pregnancy as predictor variables, including the dipstick test for proteinuria.

Results

In the present study, 336 pregnant women delivered with PE/SP (Table 1). Compared to the pregnant women without PE/SP, the pregnant women with PE/SP tended to be older, nulliparous, and have larger BMIs, medical history (CH and DM), family history of PE, higher MAPs, and proteinuria on dipstick (Table 1). The percentage of women with proteinuria at 10–13 weeks gestation who went on to develop PE and SP was 31/236 (13%) and 17/100 (17%), respectively.

Table 1
Characteristics of the participants

	PE/SP (n = 336)	Not affected (n = 8,750)	P value
Maternal age in year	32.5 (5.2)	31.9 (4.8)	0.03
Body mass index in kg/m ²	22.9 (3.8)	21.3 (3)	< 0.0001
Gestational age in week	38.8 (2)	39.2 (1.6)	< 0.0001
Chronic hypertension	100 (29.8)	238 (2.7)	< 0.0001
Diabetes mellitus (type1 or 2)	6 (1.8)	23 (0.3)	< 0.0001
Systematic lupus erythematosus	1 (0.3)	8 (0.1)	0.3
Family history of preeclampsia	17 (5.1)	242 (2.8)	0.02
Parity			
Nulliparous	220 (65.5)	4,662 (53.3)	< 0.0001
Parous with previous preeclampsia	23 (6.8)	165 (1.9)	
Parous with no previous preeclampsia	93 (27.7)	3,923 (44.8)	
Interval in year	4.6 (3.2)	3.8 (2.3)	0.01
Gestational age of last delivery in week	38.4 (2.4)	38.9 (1.8)	0.02
Conception by in vitro fertilization	30 (8.9)	477 (5.5)	0.009
Mean arterial pressure in mmHg	89.7 (11.4)	79.9 (9.1)	< 0.0001
Dipstick test for proteinuria			
Negative	226 (67.3)	7,391 (84.5)	< 0.0001
±	62 (18.5)	1,027 (11.7)	
≥'1+'	48 (14.3)	332 (3.8)	
Data are expressed as means (standard deviation) for continuous variables and n (%) for categorical variables.			
PE, preeclampsia; SP, preeclampsia superimposed on chronic hypertension.			

Table 2. Prediction Model for delivery with preeclampsia including dipstick test of proteinuria as a predictor variable

	Coefficients	95% confidence interval
Maternal age – 35 if > 35 in year	-0.11	-0.2 to -0.01
Body mass index – 21.4 in kg/m ²	-0.054	-0.104 to -0.003
Chronic hypertension	-2.3	-2.9 to -1.8
Diabetes mellitus (type1 or 2)	-1.2	-3.0 to 0.6
Systematic lupus erythematosus	-5.2	-8.2 to -2.3
Family history of preeclampsia	-1.1	-1.9 to -0.3
Parity		
Nulliparous (reference)	0	-
Parous with previous preeclampsia	-3.2	-4.0 to -2.4
Parous with no previous preeclampsia	-0.7	-1.3 to -0.1
interval – 1.8 in year	-0.12	-0.22 to -0.02
Gestational age of last delivery - 37 if > 37 in week	0.6	0.4 to 0.8
Conception by in vitro fertilization	0.1	-0.6 to 0.8
log MoM of MAP	-16.5	-20.4 to -12.6
Dipstick test for Proteinuria		
±	-0.8	-1.2 to -0.3
≥‘1+’	-2.2	-2.8 to -1.6
Intercept ^a	46.1	45.6 to 46.7

log MoM, log₁₀ transformed multiple of median; MAP, mean arterial pressure;

Broken-stick model was assumed for maternal age and gestational age of last delivery in week.

All continuous valuables were centralized to their means.

^a The mean of gestational age at delivery with PE/SP among the reference population

We fitted continuous variables to gestational age at delivery with PE (Fig. 1). We assumed a linear relationship for pre-pregnancy BMI, the interval between present and last delivery, and log MoM of MAP, and a broken stick relationship for maternal age and gestational age of last delivery. The mean gestational age at delivery with PE/SP among the reference population (35 years old, BMI 21.4 kg/m², no

medical history, no family history of PE, nulliparous, spontaneous conception, MAP 80 mmHg, negative for proteinuria) was 46.1 (95% CI; 45.6 to 46.7) weeks (Table 2).

Figure 2 shows the ROC curve of prediction of delivery with PE/SP, which was different from the bootstrap simulation result because of random sampling. The mAUC of model 1 and model 2 were 0.774 and 0.788, respectively. Regarding the prediction of delivery with PE/SP by the bootstrap simulation, mAUC of model 1 was 0.769 (95% CI; 0.741 to 0.797) and that of model 2 was 0.785 (95% CI; 0.758 to 0.812), for a difference of 0.016 (95% CI; 0.004 to 0.028) (Table 3). In model 2, the DRs at FPRs of 5%, 10%, and 20% were 40%, 49%, and 64%, respectively. Concerning the prediction of delivery with only PE, the mAUCs of model 1 and model 2 were 0.717 (95% CI; 0.686 to 0.761) and 0.734 (95% CI; 0.705 to 0.776), respectively, and the difference of mAUCs was significant (0.017 [95% CI; 0.004 to 0.034]) (Table 3). As for the prediction of delivery with GH/PE, mAUC of model 1 and model 2 were 0.709 (95% CI; 0.692 to 0.737) and 0.707 (95% CI; 0.691 to 0.737), respectively, wherein the difference of mAUCs was not significant (-0.0016 [95% CI; -0.0023 to 0.0015]) (Table 3).

Table 3
Performance of our two models for prediction of delivery with preeclampsia

		DR at FPR of		
Outcome and model	mAUROC (95% CI)	5%	10%	20%
PE/SP (n = 336/9,086)				
Model 1	0.769 (0.741 to 0.797)	37	48	62
Model 2	0.785 (0.758 to 0.812)	40	49	64
Difference	0.016 (0.004 to 0.028)			
Only PE (n = 236/8,748)				
Model 1	0.717 (0.686 to 0.761)	21	36	50
Model 2	0.734 (0.705 to 0.776)	23	35	55
Difference	0.017 (0.004 to 0.034)			
GH/PE (n = 610/8,748)				
Model 1	0.709 (0.692 to 0.737)	17	32	49
Model 2	0.707 (0.691 to 0.737)	18	31	49
Difference	-0.0016 (-0.0023 to 0.0015)			
Model 1 doesn't include dipstick test for proteinuria. Model 2 includes dipstick test for proteinuria.				
mAUROC, mean of area under the receiver operating characteristic curve; CI, confidence interval.				
FPR, false positive rate; DR, detection rate.				
PE, preeclampsia; SP, preeclampsia superimposed on chronic hypertension; GH, gestational hypertension.				

Discussion

We developed a prediction model for PE/SP using biomarkers measured during routine antenatal care visits and found that the dipstick test for proteinuria could slightly improve the prediction model for PE/SP. We could achieve better mAUROC in the prediction for delivery with PE/SP than that of only PE and GH/PE, and it did not improve when the dipstick test for proteinuria was included in the model. The competing risks model was successfully applied to an East Asian population, demonstrated by the fact that the mAUROC of our study was a better one among the studies in the systematic review,⁸ whose performance ranged from 0.61 to 0.88 with various biomarkers, most of which used logistic regression for their prediction models.

We excluded CH and SP when we conducted the secondary analyses, which investigated a prediction model for only PE and GH/PE; therefore, we cannot compare the quality among models, yet the developed model for PE/SP might have a higher fitness than models for only PE or GH/PE. Previous studies have also suggested that the pathophysiological background SP is different from that of PE^{17,18}, which was controversial¹⁹; therefore, it might be possible to develop a precise prediction model by considering PE and SP as different disorders, if a sufficient sample size was achieved. On the other hand, the dipstick test for proteinuria improved the mAUC of the prediction model of PE/SP, and only PE, while the mAUC of the prediction model of GH/PE did not change after including the dipstick test for proteinuria. That was apparently because of the criteria for each subtype; diagnosis of GH does not require proteinuria.

A previous study by Wright D, et al²⁰ used competing risks models to show the process of developing prediction models for PE. The predictor variables used by Wright D, et al²⁰ were similar to our predictor variables, so we were able to compare the relationship between each predictor variable and the gestational age at delivery with PE. Wright D, et al²⁰ assumed a broken-stick relationship between maternal age and gestational age at delivery with PE, which was consistent with our results. However, Wright D, et al²⁰ assumed a polynomial relationship between the interval between present and last delivery and gestational age at delivery with PE, whereas we assumed a linear relationship because it could fit the relationship well enough with simplicity and validity. We considered that the difference of the relationships came from the difference of ethnicity or random noise, especially in the interval between present and last delivery, which showed relatively high variance, and the relationship with gestational age at delivery with PE was not clear.

In our model, IVF was not a clear risk factor for PE, which differs from a previous study²¹ that suggested that it was a risk factor for PE in the Japanese population. We assumed the number of pregnant women conceived by IVF in our study was insufficient to assess the risk for PE. However, to develop a prediction model with high external validity, we included variables that were well-known risk factors, regardless of their statistical significance.

Our result has at least two implications. First, our model included only variables that are measured at regular antenatal visits, meaning this model can be easily applied in clinical practice. Previous studies^{9,11} have shown better AUROC using uncommon biomarkers, but as these do not prevail in clinical settings, we considered our model superior in terms of practicality to these previous models. We recommend that every pregnant woman should undertake dipstick test in their early pregnancy, promoting intensive follow-up for high-risk pregnant women throughout their gestation. Second, the inclusion of the dipstick test for proteinuria in our model may help detect severe types of PE. Considering the heterogeneous pathogenesis of PE, we can improve the prediction model for PE using the dipstick test for proteinuria as a predictor variable because we could detect pregnant women with PE who had proteinuria in early pregnancy. According to the two-stage theory, proteinuria results from kidney damage, during the process of systematic endothelial damage, so PE with proteinuria in early pregnancy may indicate a severe type of

PE^{22,23}, which is still controversial²⁴. If our model can detect a severe type of PE before its onset, even though the improvement of the mAUC was subtle (0.769 vs. 0.785), it will be useful in clinical practice.

This study selected predictor variables mainly according to the previous study, which used the competing risk model²⁰. There may be clinically common variables that can improve the prediction model such as the dipstick test for proteinuria, as we proposed, especially in East Asian population. Therefore, we hope that further studies will investigate other variables using our method.

The strength of the present study is that it was the first study to develop a prediction model for PE that includes the dipstick test for proteinuria as a predictor variable. This study also demonstrates the effectiveness of the competing risks models in the East Asian population, in that the mAUC of our study was a better one among those of other models previously investigated⁸, though the external validity of our model using a different East Asian cohort should be further investigated. In addition, as mentioned above, our model can be easily applied in clinical practice in Japan, which is a very important feature for a prediction model. However, the present study has some limitations. First, the definition of PE was different from the major definition^{13,14} because blood pressure was measured only once and diagnosed automatically by computers according to an algorithm. We assume that the improvement of the mAUC was over-estimated when the dipstick test for proteinuria was included because proteinuria was essential for diagnosis of PE in our algorithms according to the previous guideline. Second, the comparability of the dipstick test for proteinuria was not verified because of variability among manufacturers of dipstick tests²⁵, which were not consistent among the obstetric clinics and hospitals. We supposed that it could cause systematic error, as the prevalence of PE was also different among the obstetric clinics and hospitals.

In conclusion, we developed a prediction model for PE using routine antenatal care items, which was improved by the inclusion of the dipstick test for proteinuria.

Methods

Study population

The Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study (the TMM BirThree Cohort Study)^{26,27} started in July 2013 collecting in utero and subsequent exposure and outcome information to establish personalized health care and medicine, and approximately 50 obstetric clinics and hospitals in the Miyagi Prefecture participated in the recruiting process. We recruited pregnant women and children, the children's father, and grandparents between 2013 and 2017. A total of 22,493 pregnant women were included in the TMM BirThree Cohort Study. We excluded those who were not singletons ($n = 328$) or withdrew their consent ($n = 335$). A total of 12,744 pregnant women were missing the following data: diagnosis of PE ($n = 827$), dipstick test for proteinuria ($n = 3,958$), family history of PE ($n = 6,350$), and other predictor variables ($n = 1,609$), and were also excluded. Finally, 9,086 pregnant women were analyzed in our study. The present study was conducted in accordance with the Declaration

of Helsinki. The Approval was obtained from the Ethics Committee of the Tohoku Medical Megabank Organization (2013-1-103-1), and all participants gave written informed consent for study inclusion.

Prediction model

There are many studies reporting prediction models for PE⁸, which differ not only in variables but also in terms of the statistical model used. Among them, the competing risks model has demonstrated successful performance in the prediction of PE^{20,28,29}. In the competing risks model, all pregnant women are assumed to experience PE finally, but in most cases, delivery occurs before PE development and a survival time analysis, wherein delivery without PE is considered a censored observation, is conducted. One of the merits of this model is that we can easily calculate the risk of delivery with PE at any gestational age. This model has been well-validated in European countries^{20,28,29}, and was therefore applied in our study population.

Predictor variables

We included variables that were verified as risk factors for PE³⁰ and common in clinical practice. In addition, we referred to previous studies that used competing risks models for the prediction of PE^{20,28}.

Maternal basic characteristics, including age³⁰, systematic lupus erythematosus (SLE; present or absent)³⁰, diabetes mellitus (DM) (present or absent)³⁰, maternal family (mother or sisters), history of PE (present or absent)³⁰, method of conception (in vitro fertilization (IVF) or not)³⁰, parity (nulliparous, parous with previous preeclampsia, or parous without previous preeclampsia)³⁰, gestational age at last delivery^{20,28}, and interval between present and last delivery^{20,28} were self-reported by the pregnant women.

It is standard practice in Japan for pregnant women to visit antenatal care clinics or hospitals once every 4 weeks until 23 weeks gestation, once every 2 weeks from 24–35 weeks gestation, and once a week after 36 weeks of gestation. Therefore, we obtained the results of the measured blood pressure and dipstick test for proteinuria (negative, '±' or '≥1+') at 10–13 weeks gestation, when most of our population underwent their first or second antenatal visit, from medical records in these clinics and hospitals. In this process, timing of We used only the first measurement of blood pressure in the visit because there were clinics and hospitals where blood pressure was measured only once. We then calculated the mean arterial pressure (MAP)³⁰ ([systolic blood pressure + (2 X diastolic blood pressure)] / 3) and the log₁₀ transformed multiple of the median (log MoM) value of MAP. In addition, we obtained the maternal pre-pregnancy weight and height from medical records and calculated the pre-pregnancy body mass index (BMI)³⁰.

Outcome

We obtained the antenatal medical records to diagnose hypertensive disorders of pregnancy (HDP): chronic hypertension (CH), gestational hypertension (GH), and PE or PE superimposed on chronic hypertension (SP) on the basis of previous guidelines of the American College of Obstetricians and Gynecologists (ACOG)³¹, which was standard at the time of study recruitment.

We defined GH as a systolic blood pressure of 140 mmHg or more, or a diastolic blood pressure of 90 mmHg or more, on at least one visit after 20 weeks of gestation in a woman with a previously normal blood pressure, and PE as GH with proteinuria ($\geq$ '2+' on dipstick test) in at least one visit after 20 weeks of gestation. SP was diagnosed when women with CH developed proteinuria after 20 weeks gestation. These phenotypes were automatically diagnosed by computers according to an algorithm, and validated by one doctor.

Statistical analysis

Pregnant women's blood pressure in early pregnancy and the dipstick test for proteinuria were compared between those with and without the onset of PE/SP using Welch's t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

We conducted parametric survival time analysis that considered delivery without PE/SP as a censored observation²⁰. We assumed Gaussian distribution as a distribution of the survival curve. Maternal basic characteristics, MAP, and the dipstick test for proteinuria were included in our model as predictor variables. Before developing the prediction model, we examined the relationship between each continuous variable and the gestational age at delivery with PE/SP. Continuous variables were grouped, and we then plotted the effect of each group on gestational age at delivery with PE/SP. All continuous variables were centralized to their mean values before developing the model, and the gestational age at last delivery and the interval between present and last delivery were considered only among the parous women.

We compared two models: model 1 did not include the dipstick test for proteinuria, while model 2 did include the dipstick test for proteinuria as a predictor variable, considering delivery with PE/SP as the outcome. We applied five-fold cross-validation, and the area under the receiver operating characteristic curve (AUROC) was calculated. The mean of five AUROCs (mAUC) was considered as the performance of the models. We used the bootstrap method to gain the distribution of each mAUC and difference of mAUCs between the models with and without the dipstick test for proteinuria, calculating the 95% confidence intervals (CI). In addition, we calculated the detection rates (DR) at false positive rates (FPR) of 5%, 10%, and 20%.

To investigate the effectiveness of our model in other classifications, such as hypertension after 20 weeks of gestation, we conducted a secondary analysis. We excluded pregnant women with CH or SP from our study population, and calculated the mAUC and FPR considering only PE and GH/PE as the outcome. All statistical analyses were performed using R version 3.5.3 (<https://www.R-project.org/>).

Declarations

Acknowledgements

HO wrote original draft. HO, MI and TO carried out the statistical analysis. MI, TO, KM, TO, AN, FU, NI, MK, HM, JS and SK involved in acquisition, interpretation of data and review process. All authors had approved the submitted version.

The authors would like to thank all participants who consented to

participate in this study and all the staff in Tohoku Medical Megabank Organization, Tohoku University and Iwate Tohoku Medical Megabank Organization.

Additional information

The authors report no conflict of interest.

Sources of funding: This work was supported by the Japan Agency for Medical Research and Development (AMED), Japan [Grant Nos. JP20gk0110039, JP20km0105001].

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Figures

Figure 1

Relationship between gestational age at delivery with preeclampsia and each continuous variable. Effects on time to delivery with preeclampsia of log10 transformed multiple of median of mean arterial pressure (logMoM MAP), maternal age, maternal body mass index (BMI), gestation weeks at last delivery and interval between last and present delivery are shown with fitted line. We assumed A linear relationship for log MoM of MAP, maternal BMI, and the interval between present and last delivery, and a broken stick relationship for maternal age and gestational age of last delivery.

Figure 2

Receiver operating characteristic curve of prediction for delivery with preeclampsia Receiver operating characteristic curve of prediction for delivery with preeclampsia in two models. Predictor variables are mean arterial pressure and maternal basic characteristics (age, body mass index, systematic lupus erythematosus, diabetes mellitus, maternal family history of preeclampsia, method of conception, parity, gestational age at last delivery and interval between present and last delivery). Model 1 did not include the dipstick test for proteinuria, while model 2 does include the dipstick test for proteinuria. Mean of area under the receiver operating characteristic curve (mAUROC) of two models are 0.774 and 0.789, respectively.