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Predicting hypertensive disorders in pregnancy using multiple methods: Models with the placental growth factor parameter

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Abstract.
BACKGROUND: Placental growth factor (PlGF), one of the biomarkers, has a certain predictive effect on hypertensive disorders in pregnancy (HDP).
OBJECTIVE: To study the HDP prediction effect of different methods for variable selection and modeling for models containing PlGF.
METHODS: For the model containing PlGF, the appropriate range of PlGF parameters needed to be selected. Step-logistic regression and lasso were used to compare the model effect of twice range selection. The PlGF model with good predictive effect and appropriate detecting gestational age was selected for the final prediction.
RESULTS: The effect of the model containing PlGF tested at 15–16 weeks was better than the PlGF value without comprehensive screening. The sensitivity of both methods was over 92%. By comprehensive comparison, the final model of lasso method in this study was more effective.
CONCLUSIONS: In this study, a variety of methods were used to screen models containing PlGF parameters. According to clinical needs and model effects, the optimal HDP prediction model with PlGF parameters in the second trimester of 15–26 weeks of pregnancy was finally selected.

Keywords: Placental growth factor, model parameters, variable selection

1. Introduction

Hypertensive disorders in pregnancy (HDP) is an important risk factor for increasing neonatal and maternal morbidity and mortality [1–3]. Early prediction and treatment can be carried out through related risk factors [4]. Preeclampsia in HDP is one of the most serious pregnancy complications [5,6]. Studies

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Table 1
Classification of risk factors for HDP

Category	Risk factors
Basic situation	Age, Gravidity, Parity, Height, Pre-BMI
Family history	Family history of hypertension
Diseases	GDM, Diabetes mellitus with pregnancy, Pregnancy with immune system disease
The situation of this pregnancy	SBP, DBP, MAP, GA-W
Biomarkers	PlGF

Notes: Pre-BMI: Pre-pregnancy body mass index; Diseases: Existing or potential underlying medical diseases and pathological conditions; GDM: Gestational diabetes mellitus; SBP, DBP, MAP: Systolic blood pressure, Diastolic blood pressure, and Mean arterial pressure all at 11–13 weeks of pregnancy; GA-W: Weight gain during pregnancy.

have shown that placental growth factor (PlGF) was related to the diagnosis of HDP [7]. Nguyen et al. studied the predictive value of Soluble fms-Like Tyrosine Kinase 1 (sFlt-1) and PlGF for women at high risk of preeclampsia [8]. Combining maternal risk factors, mean arterial pressure (MAP), PlGF, and uterine artery pulsatility index (UTPI) for related prediction accuracy was higher [9]. Bian et al. used sFlt-1/PlGF ratio to predict the risk of preeclampsia in Asian women [10]. PlGF combined with other angiogenesis markers, such as sFlt-1, also had a certain prognostic value for preeclampsia [11,12]. There are also some controversies in related prediction research. Cnossen et al. found that the predictive value of uterine artery Doppler studies alone for early and late onset preeclampsia was very low [13]. No test could reliably predict preeclampsia, and further prospective studies were needed to prove the clinical utility of predictors [14].

A large number of foreign studies have confirmed the role of PlGF in predicting HDP. Such as using maternal factors plus biomarkers (PlGF, etc.) for prediction. But the associated clinical utility was unclear. For PlGF, one of biomarkers, the appropriate range of PlGF parameters included in the predictive model needed to be further selected. Moreover, variable screening methods were mostly based on the statistical indicator (P value), rather than comprehensive screening of risk factors. The data analysis method of this study mainly included two aspects: variable selection and model methods. Model parameters were screened based on the effects of various models containing PlGF, and several model methods were comprehensively selected to compare the prediction effects.

2. Materials and methods

2.1. Subjects

The data source of this study: 1368 cases collected from July 2015 to December 2016 provided by the Obstetrics Department of Peking University People's Hospital. After the pregnant women gave birth, according to the doctor's final diagnosis, the subjects were divided into 186 HDP group and 1182 control (normal pregnancy) group.

Exclusion criteria for overall data: pregnant women with chronic hypertension combined with pregnancy or eclampsia; cases with incomplete factors or data; singular values.

2.2. Classification of risk factors

The model parameters selected in this study were shown in Table 1.

Table 2
Normal range of PlGF value

Gestational weeks	PlGF value (pg/ml)
5–15 weeks	35
16–20 weeks	60
$>$ 20 weeks	100
Placental insufficiency raises the risk of preterm birth ($<$ 35 weeks)	High risk: $<$ 12

2.3. For PlGF parametric model

2.3.1. Preliminary screening of PlGF parameters

In this study, we reviewed the cases where serum PlGF was mainly tested twice. The gestational week of the next test (mainly starting at 15 weeks) was greater than the previous one. Therefore, 211 cases of data were preliminarily selected. Among them, 37 cases were in the HDP group (pregnant women without chronic hypertension combined with pregnancy and eclampsia); 174 cases were in the control (normal pregnancy) group. The ratio of training set to test set was 7:3. In the training set, there were 28 cases in the HDP group and 119 cases in the control group. In the test set, there were 9 cases and 55 cases in the HDP group and control group, respectively.

About the parameters of PlGF: $PlGF_1$ for the first test, $PlGF_2$ for the second test, $PlGF_{diag}$ for $PlGF_2$ minus $PlGF_1$. This study included the risk factors (without PlGF) mentioned in Table 1 and three factors related to PlGF, using step-logistic regression and lasso model to screen variables and build models. Both methods automatically screen and leave $PlGF_2$ (mainly the PlGF value of the second test starting from 15 weeks). And in the step-logistic regression test, $PlGF_2$ was not statistically significant. $P < 0.05$ has significant difference. Therefore, it was necessary to further select PlGF parameters according to the physiological changes of PlGF and effect of the prediction model.

2.3.2. Selection of the appropriate model with PlGF parameter

The main biological function of PlGF is to promote the formation of placental blood vessels [10,11]. PlGF is a kind of biomarker. Changes in serum PlGF of healthy pregnant women during pregnancy: PlGF levels are low at 5–15 weeks of gestation, and PlGF increases rapidly at 15–26 weeks, reaching a peak at 28–30 weeks of gestation.

And the main distribution of PlGF measured twice was also concentrated in 15–26 weeks. Combined with the variable screening and model effect of 2.3.1, the appropriate model with PlGF parameter could be selected. Finally, this study selected the serum PlGF test data at 15–26 weeks. The PlGF test for this study was a dry fluorescence immunoassay analyzer from Hebei Twente Biotechnology Development Co., Ltd. Table 2 showed the normal range of PlGF value provided by the company that tested PlGF in this study.

According to Table 2, the data of serum PlGF in 15–26 weeks were specifically selected. When PlGF has multiple detection values at 15–26 weeks, it generally takes a relatively abnormal value. At 15 weeks, PlGF value $\leqslant 35$ is abnormal. At 15–20 weeks (Not including 15 weeks), PlGF value $\leqslant 60$ is abnormal. At 20–26 weeks (Not including 20 weeks), PlGF value $\leqslant 100$ is abnormal. As long as the PlGF value is less than 12 pg/ml, it is preferred.

Finally, the results of this study selected data for a total of 922 cases. There were 85 cases in the HDP group (pregnant women without chronic hypertension combined with pregnancy and eclampsia) and 837 cases in the control (normal pregnancy) group. For the training set: 57 cases of HDP group, 588 cases of control group. For the test set: 28 cases of HDP group, 249 cases of control group. The ratio of the two data sets was 7:3.

Table 3
Comparison of the two models before screening

Model-$PlGF_1$, $PlGF_2$, $PlGF_{diag}$	P	AUC (95%CI)	Sensitivity	Specificity
Step-logistic regression	0.062	0.695 (0.526–0.864)	0.789	0.573
Lasso	0.008	0.776 (0.649–0.903)	0.883	0.581

Notes: $P < 0.05$ has significant difference. AUC: area under the curve; 95%CI: 95% confidence interval.

Table 4
Comparison of two models for detecting PlGF in 15–26 weeks

Model-PlGF (15–26 w)	P	AUC (95%CI)	Sensitivity	Specificity
Step-logistic regression	0.000	0.798 (0.703–0.893)	0.929	0.590
Lasso	0.000	0.807 (0.721–0.893)	0.929	0.643

Notes: $P < 0.05$ has significant difference. AUC: area under the curve; 95%CI: 95% confidence interval.

2.4. Data and statistical analysis

IBM SPSS statistics 23.0 software was used for data analysis. Step-logistic regression and lasso was used for model research in R studio (R version 4.0.1) Step-logistic regression and lasso are both regression methods in nature. Both of them have the function of automatic variable screening. The two regression methods are combined to carry out variable screening and modeling. The significance level alpha was set to 0.05. A 95% confidence interval was set in this study.

3. Results

In this study, the categories of predictive model parameters were derived from Table 1. For the model containing PlGF, the situation before the screening in 2.3.1 and after the screening in 2.3.2 was compared, as shown in Tables 3 and 4. Except for PlGF, all the other parameters (see Table 1) existed consistently before being included in the prediction model for automatic variable screening in 2.3.1 and 2.3.2.

For the models without PlGF screening in Table 3, the step-logistic regression test of $PlGF_2$ mentioned in 2.3.1 showed no statistical difference. In Table 4, both methods put the relative outliers of PlGF at 15–26 weeks into account. Each model index has been improved, and it was statistically significant to test PlGF in the step-logistic regression ($P < 0.05$). Especially the sensitivity, both methods have reached more than 92%. The final model selected the lasso method in Table 4, as shown in Table 5.

4. Discussion

Some angiogenic factors (Soluble fms-Like Tyrosine Kinase 1 (sFlt-1), placental growth factor (PlGF), and Soluble endothelin) in the second trimester may be tools for predicting preeclampsia [14]. Numerous studies have demonstrated that sFlt-1 and PlGF can play a role in the prediction of early preeclampsia in the second trimester [15]. Knudsen et al. also affirmed the independent predictive effect of PlGF [16]. The levels of sFlt-1 and PlGF in pregnant women in Malaysia could be used as biochemical indicators of gestational hypertension [17]. As a predictive marker of preeclampsia, PlGF could simplify the clinical management of preeclampsia and reduced costs [18].

This study used maternal basic factors and PlGF, and also confirmed the predictive role of PlGF in the second trimester. Based on the quality and effect of the model, comprehensive variable screening and modeling analysis and prediction were carried out.

Table 5
Final model situation

Model parameters	Coefficient
Pre-BMI	0.07051
Family history of hypertension	0.39227
Diabetes mellitus with pregnancy	0.23397
Pregnancy with immune system disease	0.04001
DBP	0.00806
MAP	0.10351
PlGF	−0.00071
Constant	−13.90915

Notes: Pre-BMI: Pre-pregnancy body mass index; DBP, MAP: Diastolic blood pressure and Mean arterial pressure both at 11–13 weeks of pregnancy.

5. Conclusion

In addition to basic statistical analysis, this research had comprehensive advantages in variable selection and model building. Maternal factors and biomarker PlGF were combined to predict. Based on the model and clinical needs, a comprehensive screening analysis was carried out to select the optimal prediction model plan containing the PlGF parameter. Finally, the PlGF value of 15–26 weeks (the second trimester) was selected for model research containing the PlGF parameter. The PlGF test in step-logistic regression was statistically significant ($P < 0.05$). Moreover, the comprehensive indicators such as area under the curve (AUC), sensitivity, and specificity of the model have been improved. In particular, the sensitivity of the two methods reached about 93%. Finally, the model parameters of lasso method were comprehensively selected for final HDP prediction. Future studies will need to increase the number of PlGF tests at full gestational age and increase the variety of risk factors.

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Conflict of interest

None to report.

References

[1] Boulet SL, Platner M, Joseph NT, et al. Hypertensive Disorders of Pregnancy, Cesarean Delivery, and Severe Maternal Morbidity in an Urban Safety Net Population. American Journal of Epidemiology. 2020. doi: 10.1093/aje/kwaa135.
[2] Wu P, Chew-Graham CA, Maas AH, et al. Temporal Changes in Hypertensive Disorders of Pregnancy and Impact on Cardiovascular and Obstetric Outcomes. American Journal of Cardiology. 2020; 125(10): 1508-1516. doi: 10.1016/j.amjcard.2020.02.029.

[3] Lowe SA, Bowyer L, Lust K, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Australian & New Zealand Journal of Obstetrics & Gynaecology. 2015; 55(5): e1-e29. doi: 10.1111/ajo.12399.
[4] Alasztics B, Gullai N, Molvarec A, et al. The role of angiogenic factors in preeclampsia. Orvosi Hetilap. 2014; 155(47): 1860-1866. doi: 10.1556/OH.2014.30042.
[5] Pennington KA, Schlitt JM, Jackson DL, et al. Preeclampsia: multiple approaches for a multifactorial disease. Disease Models & Mechanisms. 2012; 5(1): 9-18. doi: 10.1242/dmm.008516.
[6] Redman C. The six stages of pre-eclampsia. Pregnancy Hypertension. 2014; 4(3): 246. doi: 10.1016/j.preghy.2014.04.020.
[7] Ukah UV, Hutcheon JA, Payne B, et al. Placental Growth Factor as a Prognostic Tool in Women With Hypertensive Disorders of Pregnancy A Systematic Review. Hypertension. 2017; 70(6): 1228-1237. doi: 10.1161/HYPERTENSION-AHA.117.10150.
[8] Nguyen TH, Bui TC, Vo TM, et al. Predictive value of the sFlt-1 and PlGF in women at risk for preeclampsia in the south of Vietnam. Pregnancy Hypertension-An International Journal of Womens Cardiovascular Health. 2018; 14: 37-42. doi: 10.1016/j.preghy.2018.07.008.
[9] Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. International Journal of Gynecology & Obstetrics. 2019; 145: 1-33. doi: 10.1002/ijgo.12802.
[10] Bian XM, Biswas A, Huang XH, et al. Short-Term Prediction of Adverse Outcomes Using the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (Placental Growth Factor) Ratio in Asian Women With Suspected Preeclampsia. Hypertension. 2019; 74(1): 164-172. doi: 10.1161/HYPERTENSIONAHA.119.12760.
[11] Binder J, Palmrich P, Pateisky P, et al. The Prognostic Value of Angiogenic Markers in Twin Pregnancies to Predict Delivery Due to Maternal Complications of Preeclampsia. Hypertension. 2020; 76(1): 176-183. doi: 10.1161/Hypertensionaha.120.14957.
[12] Tasta O, Parant O, Hamdi SM, et al. Evaluation of the Prognostic Value of the sFlt-1/PlGF Ratio in Early-Onset Preeclampsia. American Journal of Perinatology. 2020. doi: 10.1055/s-0040-1709696.
[13] Cnossen JS, Morris RK, ter Riet G, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. Canadian Medical Association Journal. 2008; 178(6): 701-711. doi: 10.1503/cmaj.070430.
[14] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstetrics and Gynecology. 2019; 133(1): e1-e25. doi: 10.1097/AOG.0000000000003018.
[15] American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol, 2013; 122(5): 1122-1131. doi: 10.1097/01.aog.0000437382.03963.88.
[16] Knudsen UB, Kronborg CS, von Dadelszen P, et al. A single rapid point-of-care placental growth factor determination as an aid in the diagnosis of preeclampsia. Pregnancy Hypertension-An International Journal of Womens Cardiovascular Health. 2012; 2(1): 8-15. doi: 10.1016/j.preghy.2011.08.117.
[17] Nadarajah VD, Min RGLY, Judson JP, et al. Maternal plasma soluble fms-like tyrosine kinase-1 and placental growth factor levels as biochemical markers of gestational hypertension for Malaysian mothers. Journal of Obstetrics and Gynaecology Research. 2009; 35(5): 855-863. doi: 10.1111/j.1447-0756.2009.01037.x.
[18] Giardini V, Rovelli R, Algeri P et al. Placental growth factor as a predictive marker of preeclampsia – PREBIO study – PREeclampsia BIOchemical study. Journal of Maternal-Fetal & Neonatal Medicine. 2020. doi: 10.1080/14767058.2020.1792878.