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Prediction of hypertensive disorders in pregnancy based on placental growth factor

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Abstract.
BACKGROUND: The prediction of hypertensive disorders in pregnancy (HDP) mainly involves various aspects such as maternal characteristics and biomarkers.
OBJECTIVE: We aimed to study the effect of the HDP prediction model with or without placental growth factor (PlGF).
METHODS: This study used maternal factors and PlGF, and standardized the data uniformly. At 12–20 weeks, the comprehensive comparison of model quality with or without PlGF was conducted by logistic regression.
RESULTS: The area under curve and the model accuracy of the model with PlGF were higher than those of the model without PlGF. The accuracy of the model with PlGF was above 90%.
CONCLUSIONS: Adding PlGF to the model for predicting HDP improved the accuracy and effectiveness of the model. This study confirmed the predictive performance of PlGF.

Keywords: Model accuracy, placental growth factor, logistic regression

1. Introduction

Hypertensive disorders in pregnancy (HDP) is a group of diseases that coexist with pregnancy and hypertension [1–3]. It is one of the most common obstetric complications [4,5]. In order to reduce the occurrence of HDP and adverse maternal and infant outcomes, the disease needs to be effectively predicted as early as possible. The background and factors of HDP are complicated. Many researchers mainly made predictions based on the characteristics of the mother, some biomarkers (sFlt-1 (Soluble fms-Like Tyrosine Kinase 1), PlGF (Placental Growth Factor), VEGF (Vascular Endothelial Growth Factor), et al.) and other aspects [6–8]. With the development of various aspects of technology and engineering, in addition to statistical prediction methods, there are also artificial intelligence algorithms such as machine learning. Sufriyana et al. used maternal characteristics, uterine artery (UtA) doppler measurement, sFlt-1

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and PlGF in the second and third trimester of pregnancy to study the machine learning related model for predicting preeclampsia (PE) and intrauterine growth restriction [9]. Vascular biomarkers have been conducted many different types of comparative analysis [10]. In addition to simply using the value of biomarkers, there were cases where the ratio of sFlt-1/PlGF ratio was used for prediction. In 2016, the relevant prospective study was conducted in 14 European countries [11]. In 2019, the multi-center clinical study was jointly carried out in 25 Asian research centers to supplement Asian research data [12]. These studies were to verify the effectiveness of the sFlt-1/PlGF ratio in predicting the risk of PE in different populations. However, there are still controversies in some aspects about the research on biomarkers to predict HDP. Suresh et al. had doubts about the admission treatment of suspected pregnant women with PE by assessing angiogenic factors, and the clinical utility of these factors was unclear [13]. The predictive value of the sFlt-1/PlGF ratio for short-term twin pregnancy without PE and mother-infant or neonatal complications remained to be studied and verified [14]. Pluddemann and Annette found that the effect of PlGF blood examination for predicting PE still needed to continue to be evaluated for better and wider promotion [15].

There have been many studies on biomarkers, especially PlGF. But the domestic research is relatively less compared with foreign countries, and the clinical application is not explicit. PlGF serum is an invasive blood test. Compared with noninvasive parameters, obstetricians will use PlGF more cautiously. Biomarkers such as PlGF lack relevant research on the clinical outcome of mothers and infants, and are not widely used in domestic clinical examinations. Biomarkers and other maternal parameters need to be jointly applied to predict HDP. It is also necessary to combine clinical research evidence from more Chinese populations to formulate a plan that meets China's national conditions.

2. Materials and methods

2.1. Subjects

Data in this study was provided by the Obstetrics Department of Peking University People's Hospital. The data was summarized in the first half of 2013 and from July 2015 to 2018.

This batch of data was retrospectively analyzed, and the subjects were divided into HDP group and normal pregnancy group based on the final diagnosis from the doctor. Among them, there were 379 cases in the HDP group and 2409 cases in the control group.

2.2. Data preprocessing

Data exclusion criteria: chronic hypertension and other chronic diseases; suffering from other related to HDP diseases; cases with incomplete medical records. In this study, PlGF tests on pregnant women mainly focus on 12–20 weeks. In order to expand the amount of data and improve the quality of prediction, the relevant cases with the PlGF value at 12–20 weeks were comprehensively selected for analysis.

Finally, a total of 406 cases were included in the analysis. Among them, 54 cases of HDP (HDP without comorbidities) and 352 cases of Normal Pregnancy (no any disease). The basic information is shown in Table 1.

According to the structure of the existing data, the logistic regression model was selected as the research method. "Y" was a dichotomous variable. "Y = 1" indicates the pregnant woman was diagnosed with HDP. "Y = 0" represented the absence of HDP. The factors affecting HDP have both qualitative and quantitative parameters. In order to facilitate analysis, the data standards were unified and quantified. According to Table 2, related factors affecting the incidence of HDP were assigned value of "0 or 1".

Table 1
Basic information of selected data

Parameters	HDP ($n = 54$)	Normal pregnancy ($n = 352$)	P
Age	35.2 ± 4.9	30.9 ± 3.7	0.00
Height (cm)	163.7 ± 5.3	162.9 ± 4.6	0.23
Pre-pregnancy weight (kg)	60.4 ± 9.4	54.9 ± 7.5	0.00

Notes: Data are given as mean $\pm$ SD. $P < 0.05$ has significant difference.

Table 2
Assignment of basic parameters affecting the incidence of HDP

Factors	Variables	Quantification
Age	X_1	Age $<$ 35 years $= 0$; Age $\geqslant$ 35 years $= 1$
Pre-BMI	X_2	Pre-BMI $< 28 = 0$; Pre-BMI $\geqslant 28 = 1$
Family history of hypertension	X_3	No history $= 0$; With history $= 1$
Multiple pregnancy	X_4	Single tire $= 0$; twin tire $= 1$
GA-W (kg)	X_5	Pre-BMI $<$ 18.5, GA-W is "12.5–18" $= 0$;
		Pre-BMI: 18.5–23.9, GA-W is "11.5–16" $= 0$;
		Pre-BMI: 24–28, GA-W is "7–11.5" $= 0$;
		Pre-BMI $>$ 28, GA-W is "5–9" $= 0$;
		The rest of the cases: $= 1$

Notes: Pre-BMI, Pre-pregnancy BMI; BMI, body mass index; $P < 0.05$ has significant difference. The basic parameters of the model were statistically significant between HDP group and control group ($P < 0.05$). GA-W was for weight gain during pregnancy recommended by the IOM (2009). The remaining parameters were quantified according to criteria for high-risk factors considered by the obstetrician providing the data.

Table 3
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

Most of the basic maternal parameters were obtained through prenatal examinations. "Weight gain during pregnancy" was obtained from the prenatal examination data during pregnancy.

2.3. For placental growth factor

The placental growth factor (PlGF) detection in this study used a dry fluorescence immunoassay analyzer from Hebei Twente Biotechnology Development Co., Ltd. PlGF is a pro-angiogenic factor [11, 12]. And PlGF is generally measured from the 11th week when the placenta is formed, and the result is better when the 15th week starts. The PlGF serum concentration in normal pregnancy continues to rise to the third trimester, and then decreases to the end of pregnancy. The normal range of PlGF value provided by the company that detects PlGF in this study is shown in Table 3.

According to Table 3, PlGF of 12–20 weeks selected in this study was specifically assigned and quantified. For X_6 (PlGF): At 12–15 weeks, PlGF $> 35 = 0$; At 15–20 weeks (Not including 15 weeks), PlGF $> 60 = 0$; The rest of the cases: $= 1$.

2.4. Data and statistical analysis

IBM SPSS statistics 23.0 software was used for data analysis and model research. For six parameters

Table 4
Comprehensive evaluation index of two models

Model	P	AUC (95% CI)	AC
Without PlGF	0.000	0.815 (0.736–0.893)	0.867
With PlGF	0.000	0.834 (0.762–0.907)	0.906

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

including age, pre-pregnancy BMI, family history of hypertension, multiple pregnancy, weight gain during pregnancy, and PlGF, the logistic regression model of the binary "input" method in the SPSS 23.0 regression analysis was used. The significance level alpha was set to 0.05. This study set a 95% confidence interval.

3. Results

Incorporating the above-mentioned factors into the logistic regression equation to obtain two results with and without PlGF were as follows:

$$\text{LogitP (without PlGF)} = -3.081 + 0.895X_1 + 1.97X_2 + 22.786X_3 + 2.025X_4 + 0.295X_5$$
$$\text{LogitP (with PlGF)} = -3.165 + 0.875X_1 + 1.976X_2 + 22.798X_3 + 2.008X_4 + 0.27X_5 + 0.392X_6$$

Predicting HDP by the incidence probability P.

$$\text{P (without PlGF)} = \exp(\text{LogitP (without PlGF)})/(1 + \exp(\text{LogitP (without PlGF)}))$$
$$\text{P (with PlGF)} = \exp(\text{LogitP (with PlGF)})/(1 + \exp(\text{LogitP (with PlGF)}))$$

Through the logistic regression equation, the incidence probability P could be calculated, which could intuitively reflect the risk of HDP in pregnant women. ROC curve analysis was performed according to the incidence probability P. The comprehensive results of the two models are shown in Table 4.

Comprehensive indicators such as AUC and AC are more suitable for comprehensive analysis of model quality. According to Table 4, the AUC and AC of the model with PlGF were higher than those of the model without PlGF. In particular, the AC of the model with PlGF was above 90%. Therefore, adding the PlGF factor to the model for predicting HDP could make the model better.

4. Discussion

Lacerda et al. used VEGF, PlGF and sFlt-1 serum levels to distinguish active lupus nephritis and preeclampsia during pregnancy [16]. Black et al. used a multivariate screening algorithm for joint screening in the second trimester [17]. Maternal factors, mean arterial pressure (MAP), mean uterine artery pulsatility index (UtAPI), serum PlGF level in multiples of the median (MoM), and sFlt-1 level in MoM were used to predict premature delivery preeclampsia Combining information such as biomarkers (PlGF), Stepan et al. could improve the first trimester prediction and preeclampsia diagnosis [18].

In the aspect of data processing standardization, this research conducted qualitative and unified analysis. It was more in line with the results of the binary logistic regression model. Maternal basic factors combined with the biomarker (PlGF) for HDP comprehensive prediction was helpful to improve the accuracy and quality of the model. The discriminant effect was better than the prediction of a single class without PlGF.

5. Conclusion

According to the current domestic clinical needs and data, studying the role of PlGF as a biomarker. The actual role of PlGF was mainly researched in the overall prediction model. Simultaneously, combined with clinical needs and other basic maternal parameters for prediction. Based on the overall model, the comparison was made with or without PlGF. Adding the PlGF factor to the model for predicting HDP could improve the accuracy and effectiveness of the model. This study confirmed the predictive value and performance of PlGF. The amount of data and types of factors need to be increased in the future. And the data of people with HDP with complications should continue to be studied.

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Conflict of interest

None to report.

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