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ECHOCARDIOGRAPHY AND BIOMARKER-BASED REGRESSION MODELS FOR THE DETECTION OF GESTATIONAL HYPERTENSION IN PREGNANT WOMEN

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Abstract

Hypertensive disorders of pregnancy are characterized by both higher cardiovascular risk for women and more pronounced structural and functional changes of the heart. Certain biomarkers and echocardiographic parameters could be utilized in regression models for more accurate detection of the presence of those hypertensive disorders.

The aim of the study was to compare the differentiating abilities of several regression models for statistical certainty in establishing the diagnosis of gestational hypertension in pregnant women using echocardiographic parameters and biomarkers.

A prospective, single-centre, clinical-epidemiological study was conducted with the participation of 36 women with gestational hypertension and 50 maternal and gestational age-matched healthy pregnant controls. Certain echocardiographic parameters and serum biomarkers – placental growth factor (PlGF), galectin-3, high-sensitivity C-reactive protein and Interleukin-6, were analyzed for the women using ROC curve analysis and binary logistic regression.

We constructed three regression models, allowing very good differentiation between women with gestational hypertension and those with normotensive pregnancy. The model that included PlGF, left ventricular and right ventricular

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global longitudinal strain (LV GLS, RV GLS) had AUC 0.81, sensitivity and specificity of 86% and accuracy of 86%. The LV GLS and PlGF model had AUC of 0.90 with sensitivity 83%, specificity 88%, and accuracy 86%; and the LV GLS and RV GLS had AUC of 0.83, sensitivity 67%, specificity 92%, and accuracy 81%.

All three combined models showed better accuracy compared to PlGF, LV GLS, RV GLS or any other echocardiographic parameter or biomarker alone, which could be promising for their implementation in clinical practice.

Key words: gestational hypertension, regression models, placental growth factor, echocardiography, pregnancy, global longitudinal strain

Introduction. Hypertensive disorders complicate up to 10% of pregnancies worldwide [1]. The mechanisms of their development are not entirely unravelled but it is currently believed that an underlying placental incompetence causes a systemic response in the maternal organism, one manifestation of which is high arterial blood pressure [2]. Besides the obstetric problems that those conditions can lead to, numerous large-scale studies also indicate a higher future cardiovascular risk for women who suffer hypertensive pregnancies [3, 4].

Alongside the higher risk, changes in the cardiovascular structure and function appear to be more pronounced in hypertensive, rather than in normotensive pregnancies, indicating a certain pathological cardiovascular response. Numerous studies show more pronounced chamber dilation and worsened systolic and diastolic function in gravidas with hypertensive disorders. The prevalence and severity of those changes vary from study to study [5, 6]. Those findings are facilitated by the use of novel echocardiographic techniques, like the very promising speckle tracking-derived ventricular global longitudinal strain (GLS) which allows the detection of early, often asymptomatic functional changes in comparison to classic echocardiographic methods [7].

On the other hand, a variety of biomarkers have been proven to differ significantly in hypertensive pregnancies. PlGF, an angiogenetic protein, secreted from the placenta, is nowadays widely used in the prediction, diagnosis, and management of hypertensive disorders of pregnancy as its levels in those conditions are reduced compared to normal pregnancy [8]. Galectin-3 is a biomarker with a proven role in inflammation and cardiovascular fibrosis and remodelling and there are also a few studies that prove its elevated levels in preeclampsia [9, 10]. Compared to normal pregnancies, the levels of high-sensitivity C reactive protein [11] and Interleukin-6 [12] – both of them well-studies markers of inflammation, are also elevated in pregnancies complicated by gestational hypertension and preeclampsia, suggesting a pronounced inflammatory response in such pregnancies. Considering the cardiovascular involvement in those conditions and the future cardiovascular risk they pose, it is worth investigating whether combinations of biomarkers with certain echocardiographic parameters can yield regression models with good accuracy that characterize women with hypertensive pregnancies.

The aim of the study was to compare the differentiating abilities of several regression models for statistical certainty in establishing the diagnosis of gestational hypertension in pregnant women using echocardiographic parameters and biomarkers.

Materials and methods. A prospective, single-centre, clinical-epidemiological study was conducted between 15.08.2018 and 15.01.2020 at the Clinic of Cardiology, University multi-profile hospital "Sveti Georgi" Plovdiv, Bulgaria. The study was approved by the Ethics committee at the Medical University – Plovdiv and all participants signed a written informed consent.

The study group included 86 women: 36 (41.9%) of them diagnosed with gestational hypertension and 50 (58.1%) healthy pregnant controls. The women were enrolled from the Clinic of Obstetrics and Gynecology at the same hospital and some of the controls were referred by local Obstetrics and Gynecology practices. Eighty-one women had singleton pregnancies, while three women in the control group and two in the gestational hypertension group had bigeminal pregnancies. The age of the women was 29.99 ± 5.97 years, ranging between 18 to 43 years of age, the gestational age in weeks was 33.92 ± 4.76, ranging between 22 and 39 gestational weeks.

The diagnosis of gestational hypertension was established when hypertension (defined as office measured systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg at least twice over the course of minimum 4 hours apart) was registered for the first time after the 20th gestational week of pregnancy and significant proteinuria (defined as proteinuria for 24 h $\geq$ 300 mg) was ruled out for the women, using quantitative measurements during the hospitalization [13].

Exclusion criteria were extensive in order to ensure that the studied parameters would not be influenced by other factors. Women with preexisting arterial hypertension, hypertension detected before the 20th gestational week, diabetes mellitus, recent inflammatory diseases or trauma, cardiovascular diseases, active malignancies, or other serious systemic diseases were excluded from the study and so were gravidas under 18 years of age. Due to ethical considerations, there were no women whose current condition constituted an immediate obstetric or other medical emergency. No women diagnosed with growth restriction of the fetus participated in the control group.

The current weight and height of the women were measured with standardized equipment in the Clinic of Obstetrics and Gynecology. Body mass index (BMI) was calculated using the standard formula.

Biomarkers. ELISA method was used to determine the levels of the following biomarkers in sera of the women: Placental growth factor (PlFG), Interleukin-6 (IL-6), Galectin-3 (Gal-3), high-sensitivity C-reactive protein (hs-CRP). Diagnostic kits from the following manufacturers were used, respectively: BioVendor Research and Diagnostic Products, Brno, Czech Republic; Diaclone, Besançon, France; MyBioSource, Inc. San Diego, California, USA; ImmunoAssays S.A., Louvain-la-Neuve – Belgium.

Echocardiographic parameters. A thorough echocardiographic study was performed in accordance with the current echocardiography guidelines endorsed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [14,15]. The study was performed on a General Electric Vivid 9.5 ultrasound system and the parameters were analyzed with EchoPAC Clinical Workstation Software, version 201 (General Electric Medical System, Milwaukee, WI, USA). A variety of parameters reflecting chamber dimensions and ventricular function were measured. All linear measurements were taken in 2D, not M-mode. The global longitudinal strain of the RV was measured using the free wall of the right ventricle only.

Left-sided parameters were the following: indexed anterior-posterior diameter and volume of the left atrium, septal and posterior wall thickness in diastole, indexed telesystolic and telediastolic dimensions and volumes of the left ventricle (LV), left ventricular mass index, relative wall thickness, shortening fraction and ejection fraction of the LV, indexed stroke volume, cardiac output, cardiac index, medial and lateral mitral annular plane systolic excursion (MAPSE), E wave of the mitral inflow, deceleration of the E wave of the mitral annulus, medial and lateral S′ waves of the mitral annulus, e′ waves of the medial and lateral mitral annulus, the ratios E/A waves of the mitral inflow and E/e′ medial, E/e′ lateral and E/e′ mean, left ventricular global longitudinal strain (LV GLS).

Right-sided parameters were the following: indexed volume of the right atrium, right ventricular (RV) basal, mid-cavity, and longitudinal dimensions, proximal and distal outflow tract of RV, indexed telediastolic and telesystolic area of the RV, free wall of the RV, fractional area change of the RV, S′ wave of the tricuspid annulus, tricuspid annular plane systolic excursion (TAPSE), Right Ventricular Index of Myocardial Performance (RIMP), global longitudinal strain of RV (RV GLS), the ratio E/A of the tricuspid inflow, deceleration of the E-wave of the tricuspid inflow, e′ wave of the lateral tricuspid annulus, the tricuspid E/e′ and e′/a′ ratio and the acceleration time of the pulmonary valve.

Out of the analyzed parameters those that showed statistically significant differences between the controls and the women with gestational hypertension, indicating larger size and worsened function, were selected for further analyses, namely indexed volume of the left atrium, septal thickness in diastole, medial and lateral S′ waves of the mitral annulus, e′ waves of the medial and lateral mitral annulus, the ratios E/e′ medial, E/e′ lateral and E/e′ mean, left and right ventricular global longitudinal strains.

Statistical analysis was performed using IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows, SPSS Inc., Chicago, IL, USA). Findings with $p < 0.05$ were considered statistically significant. The following methods were used: test of Shapiro–Wilk, independent samples t-test of Student, two-independent samples test of Mann–Whitney-U, correlation analysis, binary logistic regression analysis, ROC curve analysis, screening tests validation criteria, the Kullback information criterion [16].

Seventeen echocardiographic parameters and biomarkers were analyzed. In order to establish the ones that have the best information value for differentiating between women with gestational hypertension and healthy pregnant women, the Kullback information criterion was used:

$$Ik(Ci) = \log \frac{P(Ci/D1)}{P\,(Ci/D2)},$$

where $Ik(Ci)$ is the Kullback information criterion, which is equal to the logarithm of the ratio of the posterior probability of Ci (the characteristic i) in the presence of diagnosis $D1$ and the posterior probability of the same characteristic in the presence of diagnosis $D2$.

Due to the fact that most of the parameters were quantitative ROC curve analysis was used to establish a cut-off value in order to transform them to qualitative. Youden's index [maximum (sensitivity + specificity − 1)] was used in choosing the cut-off value.

Results. The women from the two groups were maternal and gestational age matched. Results are shown in Table 1. PlGF, left ventricular global longitudinal strain (LV GLS), and body mass index (BMI) had the highest accuracy. Accuracy values for these parameters were between 74–80% which classifies them as good discriminators.

Information coefficients were calculated using the cut-off values of the parameters and were arranged in descending order as shown in Table 2. PlGF, IL-6, and the ratio E/e$'$ medial had the best differentiating abilities, followed by the left ventricular global longitudinal strain (LV GLS). Next, we tested combinations of the characteristics allowing for a classification of the study groups with better accuracy. Binary logistic regression was used and all 17 of the studied parameters in their categorical representation were included in the regression equation.

The procedure forward conditional was used in order to filter the weakly informative parameters and additionally we removed some of the characteristics that had low differentiating information value that correlated strongly with the more highly informative ones, also taking into account the percentage of correct classification of the regression model. In the final version of the equation the following parameters remained: PlGF, LV GLS, and RV GLS (Table 3). The percentage of correct classification of this model was 82.6%.

In order to improve the probability of correct classification using ROC curve analysis in the regression equation we used the quantitative representations of the selected three variables, instead of their categorical ones. The result was the

Table 1

Area under the curve (AUC), p values, cut-off values, and values of the criteria for the validation of screening tests of the analyzed characteristics (echocardiographic parameters and biomarkers) arranged in descending order according to accuracy

Characteristics	AUC	*p* value	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
PlGF	0.85	< 0.001	≤ 95.1	69	84	76	79	78
LV GLS	0.81	< 0.001	≥ -21.35	81	74	69	84	77
BMI	0.79	< 0.001	≥ 27.78	86	66	65	87	74
RV GLS	0.74	< 0.001	≥ -26.8	67	78	69	76	73
IL-6	0.65	0.020	≥ 5.46	47	86	71	69	70
E/e′ medial	0.71	0.001	≥ 7.47	50	84	69	70	70
S′ medial of mitral annulus	0.63	0.042	≤ 8.5	47	84	68	69	69
e′ medial of mitral annulus	0.71	0.001	≤ 11.5	78	62	60	79	69
Galectin-3	0.65	0.022	≥ 7.25	64	68	59	72	66
Septal thickness in diastole	0.71	0.001	≥ 8.5	89	50	56	86	66
S′ lateral of mitral annulus	0.69	0.003	≤ 10.5	75	60	57	77	66
e′ lateral of mitral annulus	0.68	0.005	≤ 14.5	67	66	59	73	66
e′ mean of mitral annulus	0.72	0.001	≤ 13.25	77	58	56	78	66
E/e′ mean	0.71	0.001	≥ 5.92	78	58	57	78	66
Indexed left atrial volume	0.64	0.026	≥ 23.2	61	66	56	70	64
hs-CRP	0.63	0.043	≥ 5.46	72	56	54	74	63
E/e′ lateral	0.66	0.015	≥ 4.75	86	46	53	82	62

Legend: PlGF – Placental growth factor; LV GLS – left ventricular global longitudinal strain; BMI – body mass index; RV GLS – right ventricular global longitudinal strain; E/e′ medial – the ratio of the peak velocity of the E-wave of the mitral inflow and the peak velocity of the e′-wave of the medial mitral annulus; S′ medial – the peak velocity of the S′ wave of the medial mitral annulus; e′ medial of mitral annulus – the peak velocity of the e′ wave of the medial mitral annulus; S′ lateral of mitral annulus – the peak velocity of the S′ wave of the lateral mitral annulus; e′ lateral of mitral annulus – the peak velocity of the e′ wave of the lateral mitral annulus; e′ mean – the mean of the medial and lateral peak velocities of the e′ wave of the mitral annulus; E/e′ mean – the ratio of the E-wave and the mean e′ wave of the mitral annulus; hs-CRP – high-sensitivity C reactive protein; E/e′ lateral – the ratio of the E-wave and the e′ lateral of the mitral annulus

T a b l e 2

Information coefficients of the analyzed parameters and biomarkers for differentiating the healthy controls from women with gestational hypertension, arranged in descending order

Characteristics	Cut-off	100*$I_k(C_i)$
PlGF	≤ 95.1	63.75
IL-6	≥ 5.46	52.80
E/e′ medial	≥ 7.47	49.49
LV GLS	≥ -21.35	49.11
RV GLS	≥ -26.8	48.15
S′ medial of mitral annulus	≤ 8.5	47.00
BMI	≥ 27.78	40.36
e′ medial of mitral annulus	≤ 11.5	31.11
Galectin-3	≥ 7.25	30.03
e′ medial of mitral annulus	≤ 14.5	29.24
S′ medial of mitral annulus	≤ 10.5	27.30
E/e′ mean	≥ 5.92	26.76
e′ mean	≤ 13.25	26.40
Indexed left atrial volume	≥ 23.2	25.46
Septal thickness in diastole	≥ 8.5	24.99
hs-CRP	≥ 5446	21.52
E/e′ lateral	≥ 4.75	20.07

Legend: see Table 1

T a b l e 3

Regression coefficients, OR and 95% C.I. for EXP(B) of the investigated characteristics for gestational hypertension

Characteristics	B	S.E.	Sig.	Exp(B)	95% C.I. for EXP(B)	
					Lower	Upper
PlGF ≤ 95.1	2.328	0.662	0.000	10.255	2.799	37.568
LV GLS ≥ -21.35	1.611	0.630	0.011	5.008	1.457	17.217
RV GLS ≥ -26.8	1.897	0.657	0.004	6.669	1.839	24.181
Constant	−3.030	0.663	0.000	0.048		

following binary logistic equation:

$$P = \frac{1}{1 + e^{-z}},$$

where

$$Z = -0.027\text{PlGF} + 0.342\text{LV GLS} + 0.159\text{RV GLS} + 14.410.$$

For this equation AUC equalled 0.81, and the accuracy for the cut-off ≥ 0.471 was 86% (Table 4).

Due to the fact that the right ventricular GLS is still not a standardized measurement in echocardiography [14], we composed a binary logistic equation that includes only PlGF and LV GLS:

$$Z = -0.023\text{PlGF} + 0.469\text{LV GLS} + 12.230.$$

For this equation AUC equalled 0.90 and the accuracy for the cut-off ≥ 0.509 was again 86% (Table 4).

In order to predict the presence of gestational hypertension using only echocardiographic parameters, we composed an equation of only the global longitudinal strains of both ventricles:

$$Z = 0.513\text{LV GLS} + 0.122\text{RV GLS} + 13.894$$

For this equation AUC equalled 0.83, and the accuracy for cut-off ≥ 0.548 was 81% (Table 4).

Table 4

AUCs, p-values, and cut-offs for the combinations between LV GLS, RV GLS and PlGF for the differentiation between normotensive controls and women with gestational hypertension and values of the criteria for validation of screening tests

Characteristics	AUC	p value	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
LV GLS, RV GLS and PlGF	0.92	< 0.001	≥ 0.471	86	86	82	90	86
LV GLS and PlGF	0.90	< 0.001	≥ 0.509	83	88	83	88	86
LV GLS and RV GLS	0.83	< 0.001	≥ 0.548	67	92	86	79	81

Discussion. Regression models are useful tools in medicine both to improve prediction and characterization of certain conditions [17]. Most of the models for hypertensive disorders of pregnancy combine maternal characteristics and Obstetrics-specific markers [18]. PlGF testing substantially reduced the time to clinical confirmation of preeclampsia in a 2019 study, which led to a better management of such women and to lower complication rate, which stresses the importance of these markers in the management of hypertensive pregnancies [8].

More studies are focused on preeclampsia than on gestational hypertension, although higher cardiovascular risk exists after both hypertensive disorders and the lack of proteinuria should not lead to underestimation of health risk in those women. A cohort study, encompassing data about 58 671 pregnancies proved a higher risk for the development of arterial hypertension after gestational hypertension than after preeclampsia [19]. In a 2018 study encompassing 373 pregnant women in Ghana, the use of PlGF and PAPP-A improved the prediction of gestational hypertension compared to a model with just maternal characteristics [20]. To our knowledge, this is the first study that utilized PlGF and echocardiographic parameters to present regression models characterizing women with gestational hypertension. One possible problem of regression models is the use of several biomarkers for better accuracy which is oftentimes not feasible in low and middle-income countries [18]. A potential strength of our study is that the suggested regression models combine the already established marker for poor placentation – PlGF, with echocardiographic parameters, which are readily available, safe, and inexpensive.

Conclusion. As a result of the performed analyses, we established the echocardiographic parameters (LV GLS, RV GLS) and biomarkers (PlGF) that had the best differentiation value and generated 3 binary logistic regression equations, allowing the classification of the pregnant women into one of two categories – having gestational hypertension or having normotensive pregnancy with probability of correct answers that reached 86% in two of the models.

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