ORIGINAL ARTICLE

Artificial Intelligence Modeling with Non-Invasive Hemodynamics to Predict Preeclampsia in High-Risk Pregnancy

Desarrollo de un modelo por inteligencia artificial con hemodinamia no invasiva para predecir preeclampsia en embarazos de alto riesgo

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ABSTRACT

Background: Preeclampsia (PE) is the main cause of maternal-fetal morbidity and mortality in our country. Early hemodynamic changes during pregnancy could predict progression to PE. Machine learning (ML) enables the discovery of hidden patterns that could early detect PE development.
Objective: The aim of this study was to build a classification tree with non-invasive hemodynamic variables for the early prediction of PE occurrence.
Methods: This was a prospective observational study with high-risk pregnant women (n=1155) referred by the Obstetrics division from January 2016 to October 2022 for ML training sampling, with a j48 classification tree. A total of 112 women with 10 to 16-week pregnancy and without pharmacological treatment were selected, who completed follow-up at the end of their pregnancy. The end point, PE, was a composite of preeclampsia, eclampsia, and HELLP syndrome. They were evaluated simultaneously with impedance cardiography and pulse wave velocity and with 24-h ambulatory blood pressure monitoring (ABPM).
Results: Seventeen patients (15.18%) presented PE. A predictive classification tree was generated with arterial compliance index (ACI), cardiac index (CI), cardiac work index (CWI), ejective time ratio (ETR), and Heather index (HI). A total of 93.75% patients were correctly classified (Kappa 0.70, positive predictive value 0.94 and negative predictive value 0.35; accuracy 0.94, and area under the ROC curve 0.93).
Conclusion: ACI, CI, CWI, ETR and HI variables predicted the early development of PE in our sample with excellent discrimination and accuracy, non-invasively, safely and at low cost.

Keywords: Machine Learning - Preeclampsia - Non-invasive Hemodynamics - Impedance Cardiography

RESUMEN

Introducción: la preeclampsia (PE) es la principal causa de morbimortalidad materno-fetal en nuestro país. Alteraciones hemodinámicas precoces durante el embarazo podrían predecir la evolución a PE. El machine learning (ML) permite el hallazgo de patrones ocultos que podrían detectar precozmente el desarrollo de PE.
Objetivo: desarrollar un árbol de clasificación con variables de hemodinamia no invasiva para predecir precozmente desarrollo de PE.
Material y métodos: estudio observacional prospectivo con embarazadas de alto riesgo (n=1155) derivadas del servicio de Obstetricia desde enero 2016 a octubre 2022 para el muestreo de entrenamiento por ML con árbol de clasificación j48. Se seleccionaron 112 embarazadas entre semanas 10 a 16, sin tratamiento farmacológico y que completaron el seguimiento con el término d/e su embarazo con evento final combinado (PE): preeclampsia, eclampsia y síndrome HELLP. Se evaluaron simultáneamente con cardiografía de impedancia y velocidad de onda del pulso y con monitoreo ambulatorio de presión arterial de 24 hs (MAPA).
Resultados: presentaron PE 17 pacientes (15,18%). Se generó un árbol de clasificación predictivo con las siguientes variables: índice de complacencia arterial (ICA), índice cardíaco (IC), índice de trabajo sistólico (ITS), cociente de tiempos eyectivos (CTE), índice de Heather (IH). Se clasificaron correctamente el 93,75%; coeficiente Kappa 0,70, valor predictivo positivo (VPP) 0,94 y negativo (VPN) 0,35. Precisión 0,94, área bajo la curva ROC 0,93.
Conclusión: las variables ICA, IC, ITS, CTE e IH predijeron en nuestra muestra el desarrollo de PE con excelente discriminación y precisión, de forma precoz, no invasiva, segura y con bajo costo.

Palabras clave: Aprendizaje automático - Preeclampsia - Hemodinamia no invasiva - Cardiografía de impedancia

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INTRODUCTION

Preeclampsia (PE) is one of the main causes of worldwide perinatal morbidity and mortality, and hypertensive disorders of pregnancy (HDP) are generally responsible for frequent hospitalizations, maternal-fetal morbidity and preterm birth, affecting approximately 10% of all pregnancies. (1) In addition, PE is associated with numerous disorders in the offspring of mothers with PE, mainly hypertension, diabetes and obesity. (2) The adverse results of PE can be prevented with the early use of acetyl salicylic acid (ASA) as the most efficient therapeutic strategy. Randomized studies including more than 60 000 pregnant women showed that aspirin administered at an adequate dose (≥150 mg/day) and initiated before 16 weeks of pregnancy could prevent most PE cases, especially those of early initiation and those of maternal and fetal severe disease. However, ASA treatment after this week of gestation has not shown maternal-fetal benefits. Therefore, there is urgent need of identifying women with risk of developing PE who could benefit from early ASA prophylaxis at the beginning of pregnancy. (3)

The hemodynamic adaptations during normal pregnancy allow fulfilling the greater metabolic demands to satisfy fetal requirements. (4,5) In the first and third trimester maternal physiological hemodynamics is similar to that of a non-pregnant woman. (6,7) However, in the second trimester, the metabolic demand decreases blood pressure (BP) as a consequence of vascular dilation, increasing cardiac output (CO) due to enhanced heart rate and stroke volume, with a decrease in peripheral vascular resistance (PR), generating a hyperdynamic phenotype. (8) Conversely, if this hemodynamic pattern presents in the first trimester, the risk of developing PE increases. Thus, the detection of inadequate behavior in the hemodynamic patterns at the beginning of pregnancy could prematurely predict PE development to optimize the therapeutic opportunity with ASA.

The gold standard to evaluate CO and PR is thermodilution assessment with a Swan-Ganz catheter (invasive hemodynamics), which is not applicable in "healthy" individuals and even less in pregnant women as routine complementary methods. Echocardiography has been used to identify cardiovascular adaptations during pregnancy. However, measurements require a long time, are demanding from a technical point of view and depend on the investigator. (9) For this reason, non-invasive hemodynamics evaluated by impedance cardiography (ICG) has gained relevance, especially in the evaluation of pregnant women. (10-12) Classically, the hemodynamic phenotypes of pregnancy have been defined by the behavior of two variables: cardiac index (CI) and PR, (6,7) but the information of circulatory physiology is not limited to only these two hemodynamic variables, and hidden phenotypes could be identified with non-invasive techniques considering other variables which can also be assessed with ICG. (13)

Artificial intelligence (AI) is widely used in the medical field and automatic learning, and has the potential of revolutionizing medical care, both in the general population and pregnant women, (14) as it could provide earlier and more accurate diagnoses, relieve the physicians' workload, reduce costs and deliver reference analyses to be interpreted by the different specialists acting during pregnancy. (15,16)

AI with machine learning (ML) could be the key to unblock the potential of ICG and carotid-femoral pulse wave velocity (cfPWV) evaluation in pregnancy, (17) and would allow the addition of non-invasive hemodynamic markers, beyond the classically described CI and PR in gestational hemodynamics. This would provide relevant additional information to the results at the beginning of pregnancy and could also be used as a predictive tool of associated diseases, generating a clinically relevant PE predictive algorithm to optimize the indication of ASA from the onset. (18)

Therefore, the objectives of the present study were: 1. To generate a model, using AI, of non-invasive hemodynamic phenotypic patterns for the prediction of PE in the first trimester of high-risk pregnant women, and 2. To evaluate hidden patterns beyond PVR and CO, which will consider other hemodynamic variables (flow, resistance, contractility, fluid, systolic function, left ventricular energy efficiency and arterial distensibility) in PE prediction.

METHODS

High-risk pregnant women with 10 to16-week of gestation were consecutively referred from the Obstetrics Division (Hospital San Martín, La Plata) to the Cardiometabolic Diseases Unit for BP monitoring. A pre-established BP evaluation protocol and non-invasive hemodynamics was carried out in women who had completed their pregnancy, from January 2016 to October 2022. The endpoint was the composite of PE, eclampsia or HELLP syndrome. Pregnant women under pharmacological antihypertensive treatment, previous valve diseases, congenital heart diseases, atrial fibrillation and/or dialysis were excluded from the study.

Impedance cardiography and carotid-femoral PWV (Zlogic 1.20b, Aortic 3.10, Exxer, Argentina) were performed and 24-hour ambulatory BP monitoring (ABPM) (Spacelabs 90207, USA) was fitted on the same day. (19) Impedance cardiography was carried out with the patient in dorsal decubitus position and at 3 minutes of adaptation in standing position, acquiring an average of at least 10 consecutive beats, with simultaneous carotidogram channel to solve any ambiguity between point B and point X. (11) The following hemodynamic parameters were measured: of flow: stroke volume index (SVI) (mL/beat/m2), CI (L/min/m2); of afterload: vascular resistance index (VRI) (dyn*s*cm-5), arterial compliance index (ACI) (mL/mmHg/m2); of contractility: velocity index (VI) ((1000*sec)-1), cardiac acceleration index (CAI) ((100*sec2)-1), systolic time ratio (STR) (%), ejective time ratio (ETR) (%), cardiac work index (CWI) (kg*m/m2), Heather index (HI) ohm/s2); of thoracic fluid level: thoracic fluid content (TFC) (Kohms-1); of cardiovascular performance: arterial elastance (Ea) (mmHg/mL), end-systolic ventricular elastance (Ees) (mmHg/mL), ventriculo-arterial coupling (VAC); and of arterial distensibility: cfPWV (m/sec).

The latter was measured immediately after the ICG study with applanation tonometry in the left carotid and femoral arteries, with pedometer-assessed carotid-femoral distance and average of three consecutive recordings with at least 10 beats in each recording. Twenty-four-hour ABPM was carried out defining daytime and nighttime periods according to the patient's diary. Studies were considered valid with >70 % recordings and at least 1 per hour.

Statistical analysis

Data were collected with relational database management software (Filemaker 12, 0v1, USA), which allowed exporting data of interest to a Microsoft Excel 2010 chart to be analyzed by descriptive statistics with MedCalc™ 22.009 (Belgium). Results were expressed as mean, standard deviation (SD), standard error (SE) and confidence interval (95% CI), or median and 95% CI, according to the D'Agostino-Pearson normality test. Unpaired Student's t test or unpaired Mann-Whitney test, according to normal or non-normal distribution, were used for comparisons between groups. Qualitative variables were expressed as percentages and the chi-square test or Fisher's exact test was used to compare groups, as appropriate. Statistical significance was established at $p<0.05$. A j48 classification tree (Weka 3.8.6. Waikato University, New Zeland) was used for automatic learning training sampling. The classification instances were evaluated with Cohen's Kappa index as goodness of fit of the complete model, assuming a value ≥0.7 to consider that the model was appropriate. Mean absolute error was used to indicate the estimated error, in which lower values signify a more correct model. The area under the ROC curve assessed the model's capacity to detect PE events, and its accuracy was described as percentage of well-classified instances.

Ethical considerations

All participants provided their oral and written informed consent to participate in the study, which was approved by the Research Ethics Committee of Hospital San Martín of La Plata (HSMLP2022/0079)

Sponsor

This work is part of the research protocol: "Machine learning to predict preeclampsia by non-invasive hemodynamics in high-risk pregnancy" which received financial support from the Ministry of Health of the Buenos Aires Province, through the Scholarship Program to Julieta Lanteri, awarded from the Research and Technical Cooperation Direction of the "Floreal Ferrara" Health Government School Provincial Direction. The study was registered in the Joint Health Research Commission (CCIS) (EX-2023-20132598-GDEBA-CCISMSALGP).

RESULTS

Among a total of 1155 high-risk pregnant women registered with non-invasive vascular studies, 112 were included to model automatic learning after selection and exclusion criteria, 17 with PE (15.18%). Mean age was 30 years, without difference between groups with and without PE. Pregnancy termination was premature, with a median of 35 weeks in pregnant women with PE and 38 in those without PE ($p=0.007$). In patients with PE, the frequency of early PE was low (n= 3, 17.64%), and late in most cases (n=14, 82.35%). Blood pressure in 24-h ABMP did not present differences between groups in the 24-hour, daytime, nighttime and without diagnosis of hypertension averages (Table 1). The hemodynamic variables did not show significant differences between the two groups, although there was a tendency to greater CWI ($p=0.06$) and HI ($p=0.05$), which are variables related to left ventricular contractility, in patients with PE. Also, afterload, evaluated with VRI ($p=0.05$) and TFC ($p=0.02$) was higher in those with PE (Table 2). Arterial stiffness assessed by cfPWV showed no differences. The composite endpoint (n=17) generated a supervised algorithm by classification tree where a predictive pattern with 5 non-invasive hemodynamic variables was detected (Figure 1). The main node was ACI and secondary nodes were CI, CWI, ETR and HI. It was seen that ETR and HI, which had differences between PE and non-PE, were selected by the automatic learning algorithm. However, TFC was excluded from the algorithm because it did not add predictive capacity and to optimize modeling dimensionality. From a total of 112 instances with training model, 93.75% were correctly classified. The model was adequate with 0.70 Kappa, low mean absolute value of 0.23, high positive predictive value (PPV) of 0.94, and low negative predictive

Table 1. Age, weeks of pregnancy and average daytime, nighttime and 24-h ABPM by presence or not of preeclampsia (PE) events.

Variable	PE (n=17)		Non-PE (n=95)		p
	Median	95% CI	Median	95% CI	
Age	30	25.01-36.98	31	29.00-33.00	0.928
Weeks of pregnancy	35	34.00-37.00	38	37.00-38.00	0.007
SBP 24-h ABPM	120.50	113.58-131.10	118.50	116.00-119.45	0.329
DBP 24-h ABPM	73.00	69.79-77.52	69.00	68.00-71.45	0.072
SBP ABPM daytime	124.00	116.00-131.62	122.00	120.00-125.00	0.363
DBP ABPM daytime	77.00	73.58-81.31	74.00	72.54-75.00	0.068
SBP ABPM nighttime	108.00	104.00-121.93	109.00	108.00-111.00	0.494
DBP ABPM nighttime	65.00	59.79-70.00	61.00	59.00-63.00	0.144

ABPM: ambulatory blood pressure monitoring; DBP: diastolic blood pressure; PE: preeclampsia SBP: systolic blood pressure.

Table 2. Differences between hemodynamic variables in patients with and without PE. Automatic learning variables are represented in bold characters

Variable	PE (n=17)				Non-PE (n=95)				
	Median		95% CI		Median		95% CI		p
TFC	44.91		41.43-49.87		41.46		39.78-43.49		0.026
ETR	36.28		35.71-39.25		35.99		35.08-36.67		0.210
STR	32.15		26.07-36.03		32.54		31.25-33.71		0.748
CAI	291.37		196.82-382.56		314.48		279.68-351.57		0.529
CI	4.71		4.25-5.01		4.66		4.39-4.97		0.951
ACI	1.31		1.11-1.40		1.47		1.35-1.54		0.100
SVI	62.51		46.56-71.98		62.48		59.71-69.38		0.641
CWI	6.65		5.07-7.02		5.55		5.27-5.91		0.065
VRI	1684.63		1542.56-1912.82		1507.83		1412.24-1586.64		0.054
Ea	1.04		0.91-1.27		0.96		0.92-1.06		0.204
Ees	1.34		1.17-1.56		1.25		1.21-1.32		0.169
VAC	0.75		0.66-0.89		0.74		0.71-0.78		0.932
	Mean	SD	SE	95% CI	Mean	SD	SE	95% CI	p
HI	18.12	4.11	0.99	16.00-20.23	20.96	5.69	0.58	19.80-22.12	0.052
VI	117.12	23.43	5.68	105.07-129.17	123.96	25.92	2.65	118.68-129.24	0.312
PWVcf	6.42	1.12	0.28	5.82-7.02	6.09	1.03	0.10	5.87-6.31	0.250

ACI: Arterial compliance index; CAI: Cardiac acceleration index; CI: Cardiac index; Ea: Arterial elastance; Ees: Ventricular end-systolic elastance; ETR: Ejective time ratio; HI: Heather index; PE: preeclampsia; cfPWV: carotid-femoral pulse wave velocity; STR: systolic time ratio; SVI: Stroke volume index; SWI: Cardiac work index; TFC: Thoracic fluid content; VAC: Ventriculo-arterial coupling; VI: Velocity index; VRI: Vascular resistance index.

value (NPV) of 0.35. The capacity of the model to detect PE predictive hemodynamic variables was high, with an area under the ROC curve of 0.93.

DISCUSSION

Non-invasive hemodynamic pregnancy evaluation has already been performed with reliable results. (20) However, most published studies have been made in the second and third trimester of pregnancy. We observed that CI evidenced no differences, but VRI was higher between weeks 10 and 16 in patients who later developed PE (p=0.05). Different from previous works describing hyperdynamics in the first trimester as PE predictor, (21,22) this behavior was not observed in the present work, though the inadequate hemodynamic trend in PE patients with 10 to 15-week gestational age should be pointed out. A similar interpretation was made regarding arterial stiffness, as cfPWV showed no difference because it increases in PE. (17,23) Conversely, contractility variables (CWI, with p=0.06, and HI with p=0.05) showed a statistical trend to increase in patients who developed PE, and were coherent with their classification tree selection by the ML algorithm, evidencing that, different from the classically assessed CI and VRI, occult patterns could be determined with other variables, (13) which were detected at an early gestational age.

AI is widely used in the medical field, and ML is increasingly employed in health care, prediction, and diagnosis as method to establish priorities. (24) Previous reports have used AI with ML with non-invasive hemodynamics. (25) The most frequently used algorithms were of Deep Learning with neuronal networks and classification trees for the detection of hidden patterns in great volume of data. In the present work, we chose a classification tree, as it is easier to reason, different from neuronal networks where synaptic weights shape a more complex not emulative interpretation for posterior database programming to be used in the hospital reality. The identification of patterns helps to predict and make decisions for diagnosis and treatment planning. (26) Regarding limitations, as the referral of pregnant women is more frequent since week 20, the selected sample size was not enough to analyze the incidence of PE with a logistic regression model. However, the advantage of ML is shown, as it was able to detect a hemodynamic pattern associated with PE. This suggests that AI worked supplementing traditional statistics, having the potential of revolutionizing medical care during pregnancy, by providing more accurate diagnoses, achieving better therapeutic opportunities, reducing costs of hospital medical care and improving the interpretation between specialists. (27) Another limitation is that an internal algorithm validation could not be made at the moment of the analysis. However, recruitment of pregnant women continues with the possibility of achieving this goal. In our study, AI could detect a pattern with five non-invasive hemodynamic variables that were not the classical ones (CI and VRI), and which were able to

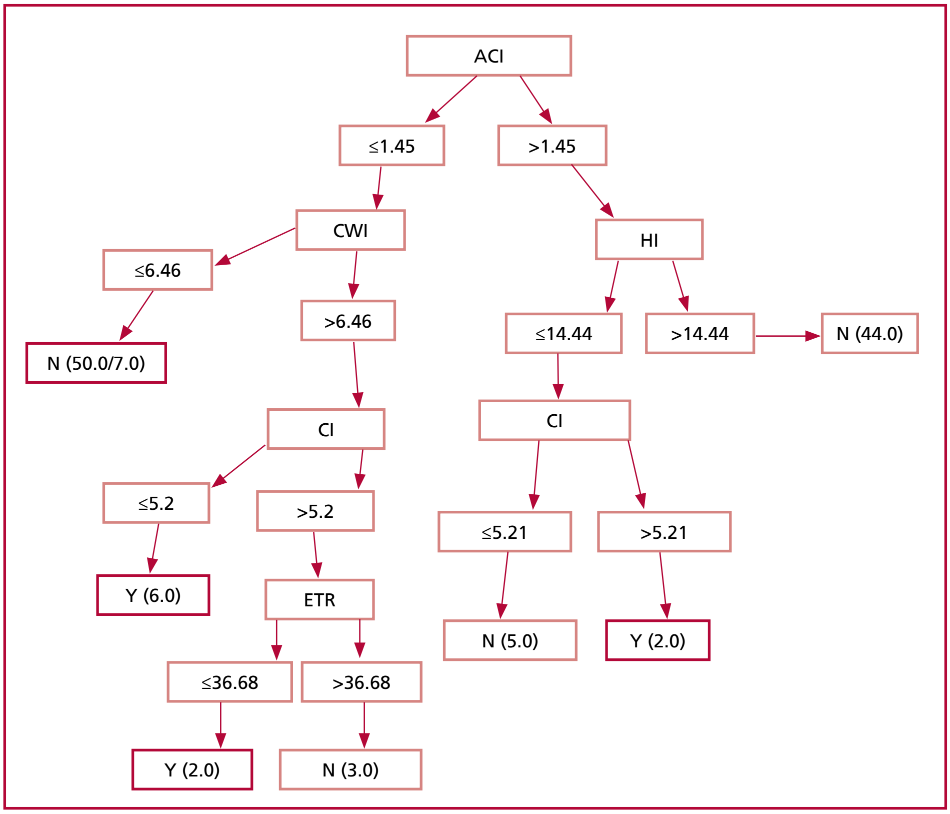

Fig. 1. Automatic learning algorithm with non-invasive hemodynamics in high-risk pregnant women with 10 to 16-weeks of gestation. Information gain from hemodynamic variables with PE in red rectangle. Abbreviations as in Table 2.

ACI: Arterial compliance index; CI: Cardiac index; CWI: Cardiac work index; ETR: Ejective time ratio; HI: Heather index; N: No; Y: Yes

predict the development of PE in early pregnancy stages. It can be observed that the initiation node was ACI and the secondary nodes corresponded mostly to contractility (HI, ETR, and CWI). This suggests that the afterload versus contractility relationship is altered prematurely between weeks 10 and 16, and still does not impact in arterial and ventricular elastances, does not affect VAC and maintains an adequate cardiovascular performance (VAC=0.75 in PE patients, Table 2). (28-31) The identification of pregnant women with hemodynamic behavior that characterizes PE between weeks 10 and 16, where the therapeutic opportunity is optimal for ASA indication, could derive more benefit from programming the hemodynamic pattern generated by ML in the databases or electronic clinical histories that automatically and timely alert on the indication of ASA with implications on maternal risk and her offspring in the future development.

CONCLUSION

Using ML, ACI, CI, CWI., ETR and HI predicted in our sample an early pattern of risk for PE development between weeks 10 to 16 of pregnancy, with excellent discrimination and accuracy, non-invasively, safely and at low cost. The early non-invasive assessment of hemodynamic variables would be a useful tool to optimize the therapeutic opportunity of ASA indication in high-risk pregnancy.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material).

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