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Predictive model for pregnancy-induced hypertension in mexican women.

Modelo predictivo de hipertensión inducida por embarazo en mujeres mexicanas

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Abstract

OBJECTIVE: To develop a predictive model for the calculation of specific risk factors per patient, for pregnancy-induced hypertension.

MATERIALS AND METHODS: We carried out a prospective cohort study of pregnant women admitted during the first trimester. The variables measured were mean arterial pressure, body mass index, mean uterine-artery pulsatility index, placental growth factor, and pregnancy-associated plasma protein A, converted to multiples of the median (MoM). Maternal variables like age, previous preeclampsia and nulliparity were also evaluated through multiple regression analysis, specific predictive models of preeclampsia and gestational hypertension risks were created using the software BRAHMS Fast Screen Pre I plus, version 3.0.0.6, risk calculation version PE 1.0.

RESULTS: A total of 132 patients were included in the study, mean age was 26.5 ± 6.6 years old, with a minimum and maximum age of 15 and 43; in 13 patients (9.9%) there was an elevated high risk for preeclampsia, in the remaining 119 (90.2%) patients, the risk was low. From the patients who developed preeclampsia near term (n = 10), high risk was predicted in2 of 3 patients (66.7%) with severity criteria; and for 1 of 7 patients (14.3%) who developed preeclampsia without severity criteria. The only case with early preeclampsia was found to be at high risk, as well as for 2 among 8 (25%) patients with late preeclampsia. The sensitivity of the predictive model for early preeclampsia was 100% with 90.4% specificity, and a LR+ of 10.4.

CONCLUSION: The predictive model is of little use in the Mexican population with multiple risk factors for preeclampsia and gestational hypertension.

KEYWORDS: Pregnancy; Hypertension, Pregnancy induced; Pregnancy Associated plasma protein A; Pre-Eclampsia; Body Mass Index.

Resumen

OBJETIVO: Desarrollar un modelo predictivo para el cálculo de factores de riesgo específicos de hipertensión inducida por el embarazo.

MATERIALES Y MÉTODOS: Estudio de cohorte, prospectivo, de mujeres embarazadas hospitalizadas durante el primer trimestre de la gestación. Variables de estudio: presión arterial media, índice de masa corporal, índice medio de pulsatilidad de la arteria uterina, factor de crecimiento placentario y proteína plasmática A asociada con el embarazo, convertida en múltiplos de la mediana (MoM), edad, preeclampsia previa y nuliparidad. Mediante análisis de regresión múltiple se crearon modelos predictivos específicos de riesgo de preeclampsia e hipertensión gestacional con el programa BRAHMS Fast Screen Pre I plus, versión 3.0.0.6, cálculo de riesgo versión PE 1.0.

RESULTADOS: Se estudiaron 132 pacientes con edad media de 26.5 ± 6.6 años y límites de 15 y 43 años. En 13 pacientes (9.9%) hubo un alto riesgo elevado de preeclampsia. En las 119 restantes (90.2%) el riesgo fue bajo. De las pacientes con

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preeclampsia, cerca del término (n = 10) se predijo un riesgo alto en 2 de 3 pacientes con criterios de gravedad; y en 1 de 7 pacientes con preeclampsia sin criterios de gravedad. Se encontró que el único caso con preeclampsia temprana era de alto riesgo, así como en 2 de 8 (25%) pacientes con preeclampsia tardía. La sensibilidad del modelo predictivo para la preeclampsia temprana fue del 100% con especificidad del 90.4% y un LR + de 10.4.

CONCLUSIÓN: El modelo predictivo es de poca utilidad en la población mexicana con múltiples factores de riesgo de preeclampsia e hipertensión gestacional.

PALABRAS CLAVE: Embarazo; hipertensión inducida por el embarazo; proteína plasmática A asociada con el embarazo; preeclampsia; índice de masa corporal.

BACKGROUND

Preeclampsia is a multi-systemic disorder which complicates 3-5% of pregnancies, and is the main cause for maternal and perinatal morbidity and mortality.[1] Data from several studies have demonstrated that systemic or generalized endothelial dysfunction is the cause for the anomalies seen in preeclampsia.[2] It is believed that the placental growth factor (PIGF) and the soluble fms-like tyrosine kinase 1 (sFlt1) are powerful angiogenic & antiangiogenic agents respectively, which contribute with the normal trophoblastic invasion and implantation.[3] It has been proposed that imbalance between these factors is crucial for the development of preeclampsia.

It has been described that a high proportion of pregnant patients who developed preeclampsia show elevated numbers of mean arterial pressure and mean uterine artery pulsatility index (IPmAUt), between the 11 to 13 weeks of gestation.[4,5] In addition, there is a reduction in placental factors such as the pregnancy associated plasma protein A (PAPP-A)[6,7] and a decrease in PIGF expression.[8,9] Furthermore, placental expression of the VEGF gene (vascular endothelial growth factor) has been shown to be much lower in women with preeclampsia compared to controls.[10] Similarly, maternal plasma concentrations of PIGF are decreased in the second trimester of pregnancy in women who subsequently develop preeclampsia, compared to women who do not.[12]

Some authors have demonstrated that PIGF is a particularly discriminatory biochemical marker for early preeclampsia in up to 33% of cases [12,13,14.] Independently, maternal medical history and some biophysical markers such as mean arterial pressure and IPmAUt have predicted early preeclampsia (before 34 weeks) in 80% of cases and late preeclampsia (after 34 weeks) in 55% [15.]In contrast, a predictive model proposed in the UK by Poon LC *et al*., which evaluated maternal factors, biophysical and biochemical markers, found a prediction of up to 93.1%, 35.7% and 18.3% for early preeclampsia, late preeclampsia and gestational hypertension, respectively.[6]

In Mexico, the predictive model of pregnancy-induced hypertension in the first trimester does not exist, however, it is very important to develop it since the prevalence of pregnancy-induced hypertension is up to 3.75%, of which up to 40% corresponds to gestational hypertension in our population, which is higher than in European countries.[16]

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Based on a combination of factors from the maternal history, mean arterial pressure and IPmAUt measurements, combined with maternal serum levels of PAPP-A and PlGF obtained between 11 and 13 weeks of gestation, a question arises: what is the level of risk and the predictive power of this model for pregnancy-induced hypertensive disease during the first trimester?

This study aims to obtain predictive models for the calculation of specific risks per patient for early preeclampsia, late preeclampsia and gestational hypertension. It is also intended to examine the performance of each of the models in the early detection of hypertension in pregnancy.

MATERIALS AND METHODS

A prospective cohort study was conducted in pregnant women treated at the first level medical units (Urban Health Centers of Culiacan Sinaloa) and referred to the Department of Perinatology and Obstetrics of the women's Hospital of Culiacan, Sinaloa, Mexico. The evaluation and follow-up of the patients until the end of their pregnancy was carried out during the period from January to December 2016.

Women who at the first trimester of pregnancy (11 to 13 weeks gestation) without complications were included. Patients with liver, kidney or coagulation disorders who received aspirin or low molecular weight heparins and prior anti-hypertensive treatment were excluded. Cases with incomplete information, inconclusive Doppler results, degraded samples or those that did not agree to continue in the study were eliminated.

The women gave their informed written consent to participate in the study, which was approved by the ethics and Research Committee of the women's Hospital of Culiacan, Sinaloa (Registry 0038).

Maternal history

The maternal medical history was obtained through a printed questionnaire applied at the prenatal visit in the first trimester of pregnancy. The questionnaire included chronological and gestational age, parity, pre-conceptional risk factors such as previous preeclampsia, previous kidney disease, pre-gestational diabetes mellitus (type 1 or 2), thrombophilias, body mass index (BMI), age over 35 years, family history of preeclampsia, chronic systemic arterial hypertension (HTcr), use of assisted reproduction methods and primipaternity. At the end of gestation, women who presented a normal evolutionary pregnancy (controls) and women who developed preeclampsia or gestational hypertension were identified. The diagnosis of preeclampsia was based on systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg, measured twice with an interval of 4 to 6 hours between each measurement, after 20 weeks gestation, accompanied by proteinuria of 300 mg/dL in a 24-hour urine sample, or proteinuria of more than +1 in urine dipstick. Early preeclampsia was defined as one that started before 34 weeks of gestation, late preeclampsia was defined as one that started after 34 weeks of gestation, while gestational hypertension was defined as the type of hypertension that occurs after week 20 of gestation without proteinuria.[17]

Biophysical markers

Doppler ultrasonography of uterine arteries

Transabdominal ultrasound of the uterine arteries was performed with color Doppler. Gestational age was calculated by ultrasound determination of crown-rump length (CRL), and fetal vitality was evaluated. To obtain the IPmAUt, Doppler indices of both uterine arteries were recorded according to the guidelines of the foundation of Fetal Medicine Barcelona (Isuog. org. Guide-

lines).[18] Values above the 95th percentile were considered to have increased resistance.

Mean arterial pressure (MAP)

Arterial pressure was determined by simple, standardized and repeated measurements with an automated sphygmomanometer (brand BEURER GmbH, Söflinger Str. 218, 89077 Ulm (Germany). The patients remained at rest for at least 5 minutes prior to reading in a sitting position, with back support and legs not crossed. 2 measurements were made on each arm at heart level. The measurements were made by the same nurse from the Perinatology service. Mean arterial pressure figures between 72 and 78 mm-Hg in the first trimester of pregnancy were considered normal.[19]

The calculation of the mean arterial pressure was made using the following formula:

(Diastolic pressure x 2 + systolic pressure) /3

Biochemical markers

The determination of these markers was done by taking 2 ml of serum obtained from maternal venous blood at the time of prenatal visit for one time.

Placental growth Factor (PIGF). B·R·A·H·M·S PIGF plus KRYPTOR Art. No.: 859.075

The serum concentration of PIGF was determined by an automated immunofluorescent assay in a Kryptor unit and the catalogue number is 859.075. (Thermo Fisher Scientific, BRAHMS GmbH, Hennigsdorf, Germany). The minimum detectable amount was < 7 pg / mL. (https://www.brahms.de/images/00_downloads/prenatal-screening/product-sheet-plgf-plus-kryptor-en.pdf).[20] the intra and inter-analysis coefficients of variation were <7.0% and <11.8%, respectively, which may vary according to the week of gestation. Baseline values from weeks of gestation 10 to 14 are 28.9 - 132 pg / ml.

Pregnancy - associated plasma protein A (PAPP-A). B·R·A·H·M·S PAPP-A KRYPTOR Art. No.: 866.075

The serum values of PAPP-A were determined by an automated immunofluorescent assay on a Kryptor equipment and its catalog number was 866.075.The functional sensitivity was 0.004 mIU / L. The intra and inter-assay coefficient of variation varies according to the week of gestation (ifu_866.075_en_brahms-kryptor-papp-a.pdf).[21] According to the supplier, the normal value for men and non-pregnant women is <14.

Statistical analysis

Data are presented as means, standard deviation, or proportions. Differences between categorical variables were determined using the c^2 test or *Fisher*'s exact test for numerical variables and the *Mann-Whitney U* test for the evaluation of continuous variables. Comparison between more than two groups was carried out with the one-way ANOVA test. The value of statistical significance was established with a value of $p<0.05$. Data were analyzed using STATA V. 13 software (College Station, Texas 77845).

Stages for the development of the model

Through a multiple linear regression analysis, a predictive model was formed with the maternal variables IPmAUt, mean arterial pressure , PAPP - A and PlGF, whose values were converted to multiples of the median (MoM) and subsequently logarithmic transformation was performed. The exam was conducted with the BRAHMS Fast Screen Pre I Plus software, v. 3.0.0.6, B·R·A·H·M·S GmbH, Hennigsdorf, Germany. Preeclampsia risk calculation version 1.0. [6]

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The risk of preeclampsia and gestational hypertension (%) was calculated from the formula: odds/(1 + odds), where odds = e ^{and} was derived from logistic regression analysis.

RESULTS

A total of 131 participants with mean age of 26.5 ± 6.6 years and BMI of 27.5 ± 6.5 kg/m^2 were evaluated. The population was divided into four groups: controls (n = 115), patients with early preeclampsia (n = 1), patients with late preeclampsia (n=8) and patients with gestational hypertension (n = 7). **Table 1** shows the characteristics of the women evaluated. It can be seen that there are significant differences between the control group and patients with late preeclampsia in the frequency of HTcr. The BMI of the control group (26.6 ± 5.9) was significantly lower than in the other groups ($p < 0.01$). The rest of the variables were not significantly different between the groups.

Table 2 shows the frequency of risk factors for preeclampsia and gestational hypertension development among controls, preeclampsia patients and gestational hypertension patients. No significant differences were observed between groups except in the frequency of previous preeclampsia between the control group (6%) and patients with preeclampsia (33.3%) ($p = 0.025$). It should be noted that there were no cases with a history of systemic lupus erythematosus, antiphospholipid syndrome or in vitro fertilization.

Table 3 shows the maternal biophysical and biochemical characteristics of the four cohort groups. The mean arterial pressure value was higher in patients with preeclampsia and gestational hypertension than in the control group ($p < 0.001$) and between controls and early preeclampsia compared to serum levels of PPAP-1-MoM.

The highest sensitivity of the predictive model was observed for early preeclampsia [100 (95%CI: 2.50-100%)] while the highest false-positive rate was obtained for gestational hypertension (10.7%). The area under the curve (ABC) was very similar in all three conditions (**Table 4**).

Table 1. Maternal characteristics of the population evaluated

Variable	Controls n = 115	Early preeclampsia n = 1	Late preeclampsia n = 8	Gestational hypertension n = 7	p Value
Age$_{(\bar{x})}$	26.3 ± 6.6	28.0	28.6 ± 7.5	28.1 ± 5.1	0.7090**
BMI$_{(\bar{x})}$	26.6 ± 5.9	32.0	36.8 ± 7.0	29.2 ± 6.4	0.0001**
HTN	3(2.6)	1(100.0)	1(12.5)	-----	0.0250§*
Chronic hypertension	21(18.3)	-----	1(12.5)	-----	0.8650*
Over 35 years old	15(13.0)	-----	2(25.0)	-----	0.4840*
Gestational diabetes	10(11.6)	-----	-------	-----	--
Severe preeclampsia	-----	1(100.0)	2(25.0)	-----	--
Mild preeclampsia	-----	-----	6(75.0)	-----	--
Macrosomic product	7(8.1)	1(100.0)	-----	-----	--
Decease	2(2.3)	-----	-----	-----	--
Resolution by caesarean section	51(58.6)	1(100.0)	8(88.9)	5(71.4)	0.7740§

n (%); §controls vs late PE.
($\bar{x}$):averages; ±: standard deviation;*Fisher's exact test; ** ANOVA test;
BMI= Body mass index; PE= Preeclampsia

Table2. Frequency of risk factors in the population evaluated

Risk factor	Controls n = 115 n (%)	PE n = 9 n (%)	P Value*	GH n = 7 n (%)	P Value*†
Previous preeclampsia	7(6.1)	3(33.3)	0.025	1(14.3)	0.386
Nulliparity	37(32.5)	1(11.1)	0.273	2(28.6)	1.000
Smoking	4(3.5)	1(11.1)	0.318	0(0.0)	1.000
Family history of preeclampsia	9(7.9)	1(11.1)	0.543	1(14.3)	0.459
History of low birth weight products	5(4.4)	0(0.0)	1.000	0(0.0)	1.000
History of DM1	1(0.9)	1(11.1)	0.140	0(0.0)	1.000
History of DM2	4(3.5)	1(11.1)	0.318	0(0.0)	1.000

†Controls *vs* GH; *Fisher's exact test; PE = Preeclampsia; GH = Gestational hypertension; DM1 = Diabetes mellitus type 1; DM2 = Diabetes mellitus type 2.

Table 3. Maternal biophysical and biochemical characteristics in the population evaluated

Variable ẋ (±)	Controls n = 115	Early PE n = 1	Late PE n = 8	GH n = 7	P Value*
CRL	61.5 ± 12.4	74.0	59.5 ± 15.2	63.0 ± 12.3	0.7674
Mean UtA-PI	1.9 ± 0.6	1.9	2.1 ± 0.8	1.9 ± .59	0.9677
Mean UtA-PI-MoM	1.2 ± 0.4	1.3	1.2 ± 0.4	1.2 ± .42	0.9703
MAP	79.4 ± 8.5	107.3	90.9 ± 6.2	91.4 ± 8.4	0.0000*
MAP-MoM	0.9 ± 0.2	1.1	1.0 ± 0.1	1.0 ± .47	0.4290
PIGF	41.7 ± 22.7	36.4	36.3 ± 26.3	42.2 ± 26.1	0.9706
PIGF-MoM	1.2 ± 0.5	0.9	1.1 ± 0.7	1.1 ± 0.5	0.9006
PAPP-A	5066.3 ± 4220.4	3060.0	3478.7 ± 3636.0	6991.8 ± 5,918.0	0.6162
PAPP-A-MoM	1.3 ± 1.0	0.7	2.1 ± 2.2	2.3 ± 1.7	0.0357‡

CRL = Crown-rump length; UtA-PI = Uterine artery pulsatility index; MoM = Multiples of the median; MAP = Mean arterial pressure; PIGF = Pacental growth factor; PPAP-A = Pregnancy-associated plasma protein A.
ẋ: average; ±: standard deviation; ‡Controls *vs* late PE. *ANOVA test; PE = Preeclampsia; GH = Gestational hypertension.

Using the established model, a high risk for preeclampsia and gestational hypertension was predicted in 13 patients (9.9%); of which one developed early preeclampsia (0.8%), two late preeclampsia (1.5%) and two gestational hypertension (1.5%).

DISCUSSION

Diagnostic methods for predicting preeclampsia currently exist, and in general, models that incorporate multiple predictive factors demonstrate better detection rates than those that use only one factor.[6] In addition, the patient's specific risk for the development of these complications is derived from algorithms that combine BMI and personal or family history of preeclampsia, mean arterial pressure measurement, IPmAUt, PAPP-A and P1GF. Also, if systematic determinations of biochemical markers were performed at population level, the probability of estimating the risk of preeclampsia would increase. [6, 9]

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Table 4. Diagnosis performance of the predictive algorithm for PE and GH

	Early PE (0.75)	Late PE (1.5)	GH (1.5)
Sensitivity (%)	100.0	25.0	25.0
Specificity (%)	90.4	90.7	89.3
LR+	10.4	2.7	2.3
LR-	0.0	0.8	0.8
Prevalence (%)	0.8	6.4	7.9
PPV	7.7	15.4	16.7
NPV	100.0	94.7	93.3
Accuracy (%)	90.5	86.5	84.2
AUC	0.54 (0.46-0.61)	0.55 (0.45-0.66)	0.551 (0.45-0.66)
FPR(%)	9.6	9.3	10.7

Prevalence (%); LR (+) = likelihood ratio for a positive test; LR(-) = likelihood ratio for a negative test; PPV = Positive predictive value; NPV = Negative predictive value; AUC = Area under the curve; FPR = False positive rate.

Models also tend to have a better predictive value for early onset preeclampsia and severity criteria preeclampsia.[6] Overall, most studies have reported modest positive predictive values. The small number of early onset preeclampsia cases and the large number of predictors in available screening models raise concerns that the described detection rates are very optimistic. To date, no model has been independently validated in prospective cohort studies. [12, 14]

The findings of this study confirm that in women who develop hypertensive disorders during pregnancy, mean arterial pressure and IPmAUt increase, and serum concentrations of PAPP-A and P1GF decrease. [22]

In both early and late preeclampsia, but not in gestational hypertension, there were significant clinical differences with respect to healthy women. The IPMAUT measurements, PAPP-1 and P1GF, were different between the patient who developed early preeclampsia and those who developed late preeclampsia. In contrast, mean arterial pressure increased in all types of hypertensive disorders, with the highest value in patients with early preeclampsia and similar among patients with late preeclampsia and gestational hypertension. Early detection of hypertensive disorders using a combination of factors mean arterial pressure, IPmAUt, PAPP - A and P1GF was better, compared to what was published by Poon *et al.,* 93%.[6] In addition, it was more effective in predicting early preeclampsia (detection rates of 100%) than late preeclampsia and gestational hypertension, with a detection rate in both, of 25%. Using the suggested combination of biophysical and biochemical parameters in this study, the detection rate is substantially higher than that determined by medical history factors alone (33%).[6] Other authors such as Akolekar *et al.*, in 2011, found a detection rate of 33% for early preeclampsia and 27.8% and 24.5% for intermediate and late preeclampsia, respectively.[23]

It should be noted that serum PIGF levels were lower in patients with preeclampsia than in patients with gestational hypertension, and in women in the control group, which is similar to what has been reported in the literature.[6] However, it should be noted that there is an inverse relationship between BMI and PIGF (r=-0.04) observed among healthy women that is lower than that of patients with preeclampsia (r=-0.51). This is explained by the different proportion of obese patients between healthy women and patients with preeclampsia, which is 25% vs 80%; this means that overweight and obesity significantly determine up to 11 times the risk of preeclampsia in our population. This situation indicates that there is an imbalance between angiogenic factors and the complement system; and that in turn are closely related to the BMI of pregnant women. Although the mechanisms by which obesity increases the rate of preeclampsia are

not clear, it is known that activated macrophages, NK cells within the uterus and the placenta, in addition to the activation in the periphery of T helper cells that produce TNF-α, IL-6, IL-17, and the antiangiogenic factor sFlt-1,as well as the B cells that produce autoantibodies agonistic to the angiotensin receptor type 1 (AT1-aa) are strong inducers of hypertension during pregnancy which could explain this disorder.[24] In addition, it has been reported that high levels of leptin, glucose, insulin and lipids in a pregnant woman with obesity influence the development of preeclampsia.[25, 26] For this reason, more research on this problem is needed.

In the present study we cannot confirm that this model is very reliable to predict preeclampsia or gestational hypertension, and it would be of utmost importance to evaluate it at the population level given its high incidence. In contrast, other authors have evaluated multiple potential biomarkers for preeclampsia prediction, whose effectiveness has been inconsistent due to the heterogeneity of the studies and limitations in sample size. The results of these studies have revealed minimal or no benefits in relation to the prediction of preeclampsia, a situation that still does not allow us to systematically use aspirin in low doses in women at high risk of developing preeclampsia.[16,27,28,29,30]

To the best of our knowledge, this is the first study conducted in Mexican women in the first trimester of pregnancy, which is reliable to identify patients who will develop preeclampsia and gestational hypertension, however, the main limitation of the study was that the logistic regressions were not robust and therefore the conclusions can only be used as hypotheses rather than as a clinically useful result and this does not allow us to suggest the proposed model as a predictive test of development of the disease in the general population of pregnant women in the first trimester.

Evaluation of the proposed model, in multicenter and large-scale studies, would allow early identification and management of pregnant women at risk of developing the disease

CONCLUSION

The predictive risk model it is not effective or useful for the prediction of preeclampsia and gestational hypertension in our population. There are still no studies that uniformly support the use of the predictive model for the development of preeclampsia to justify its use.

Conflicts of interest

This study was kindly supported by Thermo Fisher Scientific and the only contribution was the provision of free kits including Cal and QC (45 PlGF and PAPP-A) and that these kits were shared through Absten.

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