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Trabajo Original

Multiple-parameter screening and prevention of preeclampsia: Evaluation of a protocol implemented at Hospital Universitario Puerta de Hierro

Cribado multiparamétrico y prevención de la preeclampsia. Evaluación del protocolo implantado en el Hospital Universitario Puerta de Hierro

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Abstract

Objective: To evaluate the implementation in our center of a preeclampsia risk screening protocol in a low-risk population combined with preventive treatment (aspirin, 100 mg/d) by evaluating the variation in the incidence of preeclampsia. To validate the analysis tool and its predictive strength.

Material and methods: We studied 310 patients divided into 2 groups: 138 controls (TR) and 172 patients who had undergone screening and received preventive treatment (CI). We collected demographic data, gestational age at consultation, obstetric history, reproductive method, risk factors for preeclampsia (hypertension, diabetes, BMI, kidney disease, and coagulopathy), use of aspirin as preventive therapy, and data on the outcome of pregnancy (hypertension, proteinuria, diagnosis of preeclampsia, and complications). In the CI group, we also recorded the risk of preeclampsia. This was calculated retrospectively in the TR group.

Results: The protocol had 80% sensitivity and 98.4% specificity. The incidence of preeclampsia was 3.62% in the TR group and 0.58% in the CI group (p=0.053), with an OR of 0.155 (0.017-1.34). Among patients with a high risk, 66.7% developed preeclampsia in the TR group and 9.1% in the CI group (p=0.027), with an OR of 0.05 (0.04-0.57) and a number needed to treat of 1.74.

Conclusions: The high sensitivity and specificity of the analytical tool make it adequate for screening. The protocol reduces the incidence of preeclampsia in high-risk patients, even if that difference was not significant at the level of the study population.

Key words:

Preeclampsia. Screening. Preventive treatment. Acetylsalicylic acid. Low obstetric risk.

Resumen

Objetivo: evaluar la implantación, en nuestro centro, de un protocolo de cribado del riesgo de preeclampsia en población de bajo riesgo obstétrico, combinado con tratamiento preventivo con 100 mg diarios de ácido-acetilsalicílico, mediante el análisis de la variación de la incidencia de preeclampsia. Validar la herramienta utilizada, analizando su capacidad predictiva.

Material y métodos: se estudiaron 310 pacientes, distribuidas en dos grupos: 138 controles (TR) y 172 con cribado y tratamiento preventivo (CI). Se recogieron datos demográficos, edad gestacional en consulta, historia obstétrica, método reproductivo, factores de riesgo de preeclampsia (hipertensión, diabetes, IMC, nefropatía y coagulopatía), toma de ácido-acetilsalicílico de forma preventiva y datos del final de la gestación (hipertensión, proteinuria, diagnóstico de preeclampsia y complicaciones). En el grupo CI se recogió el índice de riesgo, y en el grupo TR se calculó de forma retrospectiva.

Resultados: la herramienta obtuvo una sensibilidad del 80% y una especificidad del 98,4%. La incidencia de preeclampsia resultó del 3,62% en el grupo TR frente al 0,58% en el grupo CI (p=0,053), con una OR de 0,155 [0,017-1,34]. Entre las pacientes con índice de alto riesgo, un 66,7% del grupo TR presentó preeclampsia, frente a un 9,1% del grupo CI (p=0,027), con OR 0,05 [0,04-0,57] y una NNT de 1,74.

Conclusiones: la herramienta utilizada tiene elevada sensibilidad y especificidad, resultando útil como cribado. El protocolo implantado reduce la incidencia de preeclampsia en pacientes con índice de alto riesgo, aunque la variación a nivel poblacional no fue significativa.

Palabras clave:

Preeclampsia. Cribado. Tratamiento preventivo. Ácido acetilsalicílico. Bajo riesgo obstétrico.

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INTRODUCTION

Preeclampsia is a complication of pregnancy and a hypertensive state of pregnancy. It is defined as a progressive multisystemic abnormality that is characterized by the onset of hypertension and proteinuria in a previously normotensive pregnant woman (>20 weeks). However, proteinuria is not currently considered an exclusion criterion, providing that the patient has data suggestive of target organ dysfunction (1).

Current diagnostic criteria are as follows:

- Hypertension: Systolic arterial pressure (SAP) ≥140 mmHg or diastolic arterial pressure (DAP) >90 mmHg on 2 occasions for at least 4 hours in a previously normotensive patient.
- Proteinuria: >300 mg in urine at 24 hours or protein-creatinine ratio >0.3, or positive test strip in the absence of quantitative methods.

In the absence of proteinuria, the presence of de novo hypertension is considered diagnostic of preeclampsia if accompanied by any of the following criteria:

- Thrombocytopenia: Platelet count <100,000/µL.
- Kidney failure: Serum creatinine concentrations >1.1 mg/dL or an increase of ≥100% in the absence of previous kidney disease.
- Liver dysfunction: Increase of twice the upper limit of normal for transaminases in blood.
- Pulmonary edema.
- Visual symptoms or central nervous system abnormalities.

Preeclampsia affects 2-8% of pregnancies throughout the world, although there is considerable variability by region. Thus, the incidence is 5.6% in Africa, whereas in the Mediterranean it is approximately 1-3% (2).

Although preeclampsia is not a common complication of pregnancy, it must be evaluated, since it is responsible for approximately 10-15% of deaths related to pregnancy (3), with a mortality rate of 6.4/10,000 cases (4). Preeclampsia is also a risk factor for intrauterine growth restriction and preterm birth (5).

Given that hypertensive states of pregnancy are one of the main causes of maternal death in Europe (6), their prevention is a key objective if we are to reduce maternofetal mortality.

Different combinations of treatment have been proposed for the prevention of preeclampsia, mainly nutritional supplements such as magnesium, folic acid, and omega-3. The various drugs used for the same purpose include nitrates, progesterone, diuretics, and low-molecular-weight heparin (LMWH). However, none of these lines of treatment has proven useful for the prevention of preeclampsia; therefore, their administration is not currently recommended (6). In contrast, many studies from the last 10 years conclude that low-dose aspirin (75-100 mg daily) can prevent preeclampsia during pregnancy, and many meta-analyses have evaluated its effectiveness (7-10). The Cochrane study (8), which is one of the most complete to date, concluded that the use of low-dose aspirin reduces the risk of preeclampsia by 17%, the relative risk (RR) of preterm birth by 8%, and the probability of fetal or neonatal death by 14%.

The current NICE guidelines (6) and the US Preventive Services Task Force (10) recommended aspirin for the prevention of preeclampsia, and the most recent studies set a threshold for initiation of treatment before week 16, when aspirin could favor appropriate placentation (9).

Furthermore, the most recent meta-analyses rule out the possibility that aspirin is associated with maternofetal complications such as placental abruption and perinatal death and even point to a reduction in the rate of the latter (10). Current guidelines, on the other hand, recommend avoiding overtreatment of pregnancy women by reserving prescription for those at highest risk (6-8,10).

Early assessment of the risk of preeclampsia is a key challenge in prenatal diagnosis, with various strategies currently available. These include protocols based exclusively on the identification of risk factors associated with the development of preeclampsia (11,12), which include clotting disorders, previous preeclampsia, chronic arterial hypertension (AHT), pregestational diabetes, obesity, and the use of assisted reproduction. In addition, various combinations of parameters have been developed to stratify the risk for pregnant women; these often include biochemical markers such as PAPP-A or antiangiogenic placental growth factor (PlGF), in combination with data from the mother's clinical history and Doppler ultrasound findings for the uterine arteries. Such is the case of the protocol developed by the Fetal Medicine Foundation, which includes determination of PlGF in maternal serum (13).

Since 2009, professionals at Hospital Clinic de Barcelona (HCB), Barcelona, Spain have been using a method for screening for the risk of preeclampsia in low-risk pregnant women (14). The method is based on the following:

- Epidemiological data: Parity, previous preeclampsia, chronic AHT, kidney disease, clotting disorders, pregestational diabetes, and ethnicity of the patient.
- Patient's biometric data: Age, height, and weight.
- Ultrasound data: Crown-rump length (CRL) and mean uterine artery pulsatility index (UtA-PI) during the first trimester.
- Biomarkers: PAPP-A measured between weeks 8 and 12 of pregnancy.
- Physical examination: SAP and DAP during the first-trimester visit.

This method makes it possible to stratify the risk of preeclampsia before week 16 of gestation in order to apply preventive treatment based on the administration of low-dose aspirin (15). The protocol, which does not include detection of markers not included in routine antenatal

diagnosis, was recently validated and yielded favorable results when applied in the south of Europe (16).

Hypothesis and objectives

The hypothesis of this study was that protocol-based screening of the risk of preeclampsia in low-risk pregnant women reduces the incidence of the complication by identifying patients with a high probability of developing preeclampsia, thus enabling preventive treatment with aspirin.

The hypothesis was tested by implementing a preeclampsia screening protocol in low-risk pregnancies at Hospital Universitario Puerta de Hierro (HUPHM), Madrid, Spain based on the preeclampsia staging tool from HCB. In the case of high risk (<1/70), the patient was prescribed 100 mg of aspirin daily before the 16th week of gestation.

We investigated the variation in the incidence of preeclampsia before and after application of the strategy in order to determine the ability of the tool to classify women as low-risk and high-risk.

MATERIAL AND METHODS

We performed a retrospective observational study based on computerized clinical histories of patients from HUPHM between October 2016 and March 2017. The study was performed using the SELENE® electronic platform (Cerner Corp.).

We selected all patients attended between May 2015 (TR group), before implementation of the protocol, and May 2016 (CI group), once the preeclampsia prevention strategy was adopted in the low-risk pregnancy obstetrics clinic at HUPHM. We only included patients who attended before week 16 of gestation, when, according to the protocol, the patient undergoes screening for preeclampsia. We excluded patients who had not had a complete follow-up until the end of their pregnancy at HUPHM, as well as those with multiple pregnancies, those who had received treatment with LMWH or aspirin, and those whose data were incomplete. The final sample comprised 310 patients. The selection criteria are shown in Figure 1.

We collected the clinical history number and age and, after ensuring that the patient's file data were anonymous, recorded gestational age at the visit, number of term and preterm pregnancies, number of previous miscarriages, and number of live births. We also recorded the method of reproduction used, the patient's obstetric history, and risk factors for preeclampsia (chronic AHT, pregestational diabetes, body mass index, chronic kidney disease, and clotting disorders). We determined whether the patient had been prescribed preventive therapy with aspirin (100 mg daily). Lastly, we collected data on the end of pregnancy, namely, AHT, proteinuria (and protein-creatinine index [PCI] where applicable), diagnosis of preeclampsia, and possible presence of complications of preeclampsia.

In the 172 patients in the CI group who had undergone screening for preeclampsia according to the protocol, we also recorded the risk index and stratified the risk as low or high.

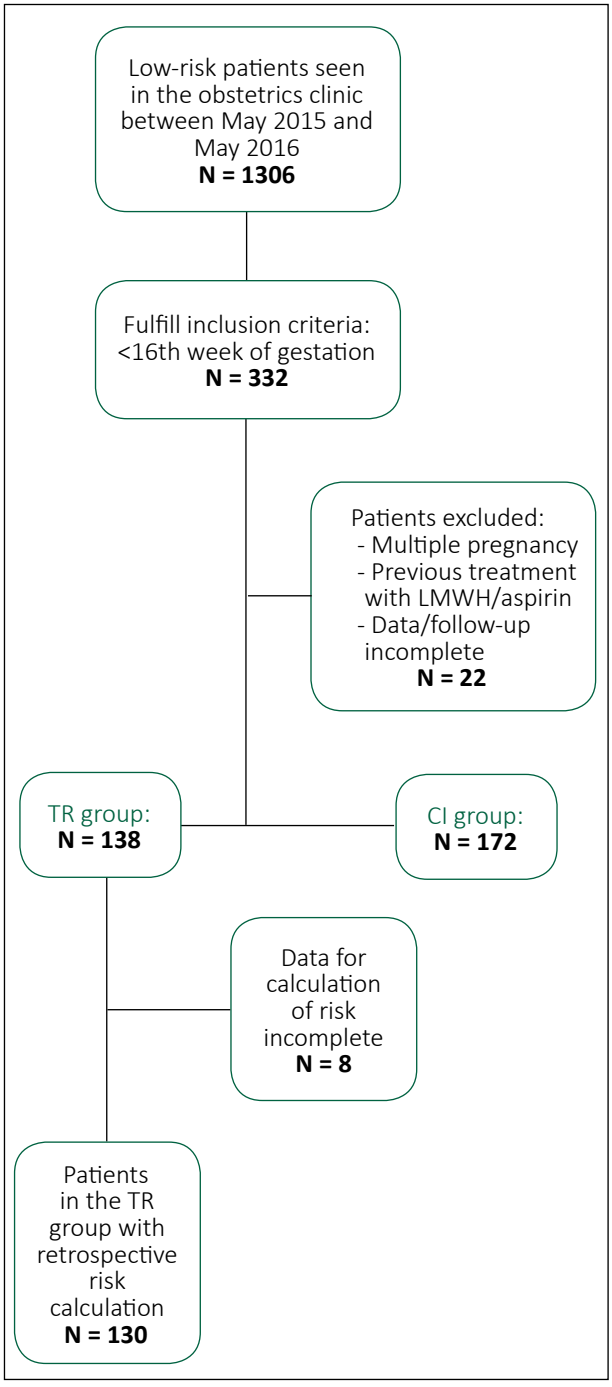

Figure 1. Patient flow chart.

In the case of the 138 patients in the TR group, who did not undergo screening, we collected the data necessary for a retrospective calculation of risk: Parity, previous preeclampsia, chronic AHT, kidney disease, clotting disorders, pregestational diabetes, ethnicity, height, weight, CRL in the first-trimester ultrasound, UtA-PI during the first trimester, PAPP-A measured between weeks 8 and 12 of gestation, and SAP and DAP during the first trimester. These data were used to calculate the risk for patients who did not undergo protocol-based screening. As data were missing for 8 patients, our investigation of risk was restricted to 130 women. The case report folder can be seen in Appendix I.

The statistical analysis was carried out using STATA v14-2 for Windows. We calculated the frequency of the contingency variables and the median (IQR) for the qualitative variables. We then evaluated homogeneity in the TR and CI groups using the Pearson χ^2 test in the case of the contingent variables and the Mann-Whitney test in the case of the qualitative variables. We also evaluated the variation in preeclampsia in the TR and CI groups using the odds ratio (OR) and RR and calculated the absolute risk reduction (ARR) and relative risk reduction (RRR). In addition, we calculated the variation in preeclampsia for high-risk patients between the TR and CI groups using the Pearson χ^2 test. Lastly, we analyzed the sensitivity and specificity of the test for detection of the risk of preeclampsia both in the TR group and in the CI group.

The present study was approved by the Clinical Research Ethics Committee of HUPHM in November 2016 (Appendix II).

RESULTS

The baseline characteristics of the patients and their stratification by groups can be consulted in Table I. Mean age was 34 years in the TR group compared with 33 years in the CI group (p=0.058). High risk was detected in 6 cases (4.62%) and 11 cases (6.40%), respectively (p=0.506). Similarly, we found no patients who received preventive treatment with aspirin in the TR group; in the CI group, 12 patients (6.97%) were treated with aspirin (p=0.002). In the TR group, 4 of the 6 patients considered high-risk fulfilled the criteria for preeclampsia at the end of pregnancy, as did 1 patient who had not been considered high-risk. Furthermore, in the CI group, of the 11 high-risk patients (6.40%), 1 (0.58%) fulfilled the criteria for preeclampsia, with no further patients fulfilling the criteria for preeclampsia in the sample. Thus, overall, the incidence of preeclampsia was 3.62% in the TR group compared with 0.58% in the CI group (p=0.053, Pearson chi-square) (Figure 2).

The median PCI in the TR group was 0.365 (0.31-1.51); in the CI group, the only patient with preeclampsia had a PCI of 1.12. In the overall population, this was 0.38 (0.31-1.51) (p=0.617). Similarly, all of the patients in the sample had preeclampsia after week 37, with a general median of 38+5 (37+6 to 39+4); the median presentation was 38+3 (37+6 to 39) in the TR group; the only case diagnosed in the CI group was at week 38+4 (p=0.380).

The calculation of the OR applied to the variation in the presentation of preeclampsia in both groups yielded a result of 0.155 (0.017-1.34); the RR was 0.16 (0.018-1.36) (p=0.053). Similarly, as a possible confounder based on patient age was found between the TR and CI groups—despite there being no statistically significant difference between the groups—an OR stratified by age was calculated (0.158 [0.018-1.37]) (p=0.095). An ARR of 0.030 was found between the TR and CI groups, that is, a 3% reduction in risk (p=0.053). The number needed to treat in the general population was 34.

Furthermore, we evaluated the variation in preeclampsia in the high-risk patients (Table II). In the TR group, 66.7% of patients presented preeclampsia while in the high-risk category, whereas in the CI group, 9.1% of patients presented preeclampsia, that is, an ARR of preeclampsia of 57.6% (p=0.027) (Figure 3). Similarly, we obtained an OR of 0.05 (0.04-0.57) in the high-risk group and an RR of 0.14 (0.02-0.96) (p=0.027). These measures of effect were used to identify an RRR of 86% and a number needed to treat of 1.74.

The sensitivity and specificity of the test for detecting the risk of preeclampsia were determined in the TR group

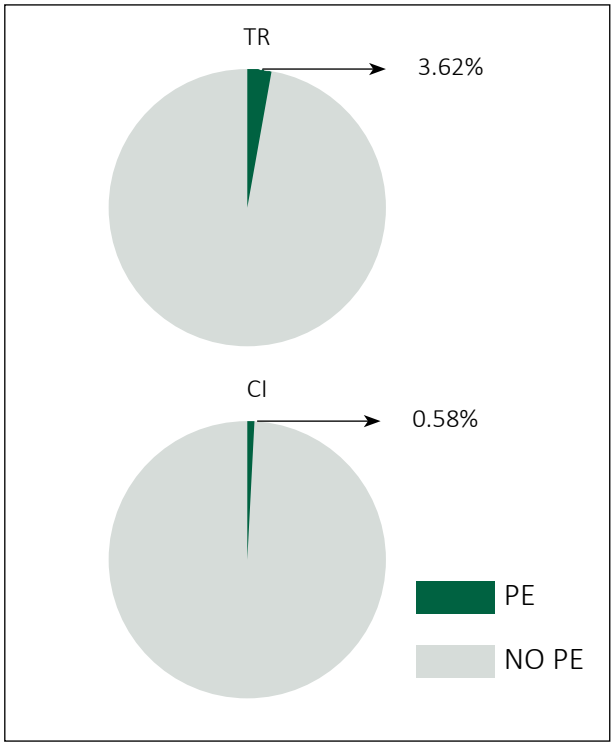

Figure 2. Incidence of preeclampsia in the TR and CI groups.

Table I.
Clinical and epidemiological characteristics by group

	No screening (TR)	Screening (CI)	Total	p
	N = 130	**N = 172**	**N = 302**	
Risk, No. (%)				**0.506**
High	6 (4.62%)	11 (6.40%)	17 (5.63%)	
Low	124 (95.38%)	161 (93.60%)	285 (94.37%)	
	N = 138	**N = 172**	**N = 310**	
Median (IQR) age	34 (31-38)	33 (29-37)	34 (30-37)	**0.058**
Median (IQR) GA at visit	12^{+0} (10^{+4}-14^{+5})	14^{+2} (11^{+4}-14^{+6})	13^{+4} (10^{+6}-14^{+6})	**< 0.01***
Median (IQR) BMI	22.55 (20.6-25.4)	22.35 (20-25)	22.4 (20.1-25.1)	**0.193**
Assisted reproduction, No. (%)	5 (3.62%)	9 (5.23%)	14 (4.52%)	**0.498**
IVF	4 (2.90%)	7 (4.07%)	11 (3.55%)	**0.580**
Previous pregnancies, No. (%)				**0.543**
0	60 (43.48%)	83 (48.26%)	143 (46.13%)	
1	62 (44.93%)	67 (38.95%)	129 (41.61%)	
2	11 (7.97%)	18 (10.47%)	29 (9.35%)	
3	4 (2.90%)	3 (1.74%)	7 (2.26%)	
> 3	1 (0.72%)	1 (0.58%)	2 (0.64%)	
Miscarriages, No. (%)				**0.795**
0	103 (74.64%)	133 (77.33%)	236 (76.13%)	
1	25 (18.12%)	31 (18.02%)	56 (18.06%)	
2	8 (5.80%)	6 (3.49%)	14 (4.52%)	
3	2 (1.45%)	2 (1.16%)	4 (1.29%)	
Induced abortion, No. (%)	8 (5.80%)	18 (10.47%)	26 (8.39%)	**0.155**
Clinical history, No. (%)				
Previous preeclampsia	2 (1.45%)	1 (0.58%)	3 (0.97%)	**0.438**
Chronic AHT	1 (0.72%)	1 (0.58%)	2 (0.65%)	**0.876**
Pregestational diabetes	0 (0%)	1 (0.58%)	1 (0.32%)	**0.370**
Chronic kidney disease	0 (0%)	0 (0%)	0 (0%)	-
Clotting disorders	1 (0.72%)	0 (0%)	1 (0.32%)	**0.263**
Preventive aspirin, No. (%)	0 (0%)	12 (6.97%)	12 (3.87%)	**0.002***
End of pregnancy, No. (%)				
AHT	6 (4.35%)	1 (0.58%)	7 (2.26%)	**0.027**
Criteria for preeclampsia	5 (3.62%)	1 (0.58%)	6 (1.94%)	**0.053**

*GA, gestational age; BMI, body mass index; IVF, in vitro fertilization; AHT, arterial hypertension; *Statistically significant difference.*

(80% and 98.4%, respectively, with an area under the ROC curve of 0.892 [0.696-1]) (Figure 4).

DISCUSSION

The objective of the present study was to evaluate a protocol aimed at screening for the risk of preeclampsia. The protocol was based on a tool developed at HCB and analysis of patients in whom the prevention strategy was implemented.

Patients were divided into 2 groups: TR, with no screening; and CI, with protocol-based screening before the 16th week. Analysis of the clinical characteristics and epidemiological data collected (Table I) revealed no statistically significant differences. While the median age was slightly different in both groups (lower in the CI group), this difference did not have sufficient statistical power to be considered a confounder. The variation in the date of the visit could be due to the fact that whereas the women in the TR group attended the standard first-trimester visit (around week 12), those in the CI group were scheduled again after that visit to calculate the risk of preeclampsia (around week 14).

As both groups were homogeneous, we were unable to identify confounders explaining the differences between the groups except for those arising from the study variables, namely, protocol-based screening and treatment with 100 mg of aspirin in the case of an index <1/70. In addition, we were unable to find patients in the TR group who had previously received preventive treatment with aspirin.

Collection of obstetric data at the end of pregnancy revealed that, according to the current classification (17), none of the patients had severe preeclampsia and that all of the symptoms appeared late (after week 37). Furthermore, in the overall sample, all patients diagnosed with preeclampsia had proteinuria, with a median PCI of 0.38 (0.31-1.51). No other symptoms were detected. Similarly, no patients in the CI group were diagnosed with preeclampsia without having been previously classed as high-risk. In contrast, the retrospective calculation of the risk in the TR group did in fact conclude that one of the patients who

Table II.
Obstetric outcomes in the TR and CI groups and incidence of preeclampsia

		No preeclampsia	Preeclampsia
TR	**Low risk**	123 (99.19%)	1 (0.81%)
	High risk	2 (33.3%)	**4 (66.7%)**
CI	**Low risk**	161 (100%)	0 (0%)
	High risk	10 (90.91%)	**1 (9.09%)**

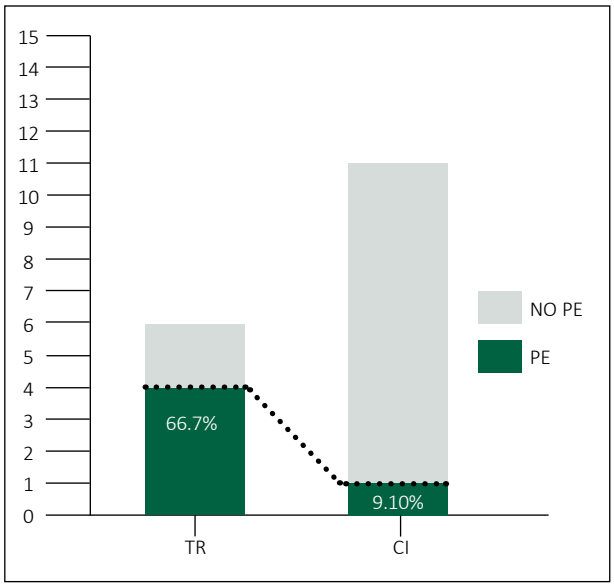

Figure 3. Variation in the incidence of preeclampsia in patients with a high risk index according to preventive treatment.

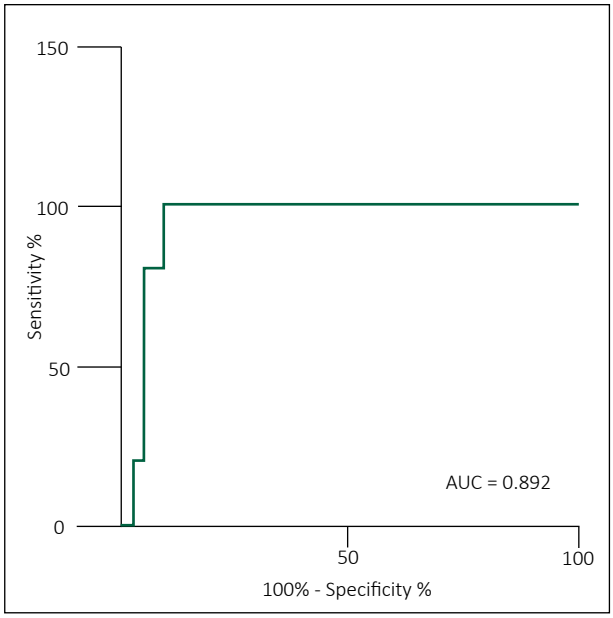

Figure 4. Receiver operating characteristic curve of the screening tool.

finally presented preeclampsia would have been missed according to the protocol used and, therefore, would not have received preventive treatment with aspirin.

The protocol had high sensitivity and specificity (80% and 98.4%) in the TR group. The ROC curve can be seen in Figure 4; the AUC obtained shows the high potency of this tool for detecting the risk of preeclampsia. These results are consistent with those obtained by the research team of HCB in the validation of their protocol (16).

As for the general variation in preeclampsia between the study groups (Figure 2), we found no statistically significant differences that could account for the reduced number of cases of preeclampsia between the groups based on the protocol. The incidence of preeclampsia in the control group (TR) was 3.62%; this is consistent with findings from previous studies in patients at HUPHM (18) and from epidemiological studies performed in the Mediterranean area (2). In contrast, the incidence calculated in the CI group after implementation of the protocol-0.58%-is lower than reported elsewhere. The size of the study sample seems to be responsible for the fact that there were no significant differences with respect to reduced incidence of preeclampsia in the study population. However, the fact that the statistical value was almost significant (p=0.053) leads us to believe that a subsequent evaluation covering a larger sample could reveal greater evidence in favor of the effect of this protocol on the incidence of preeclampsia.

The calculation of the OR and RR revealed that belonging to the CI group implied a more then 6-fold reduction in the risk of presenting preeclampsia. In addition, this finding remained unaltered when the calculation was made based on patient age. This reduced risk in patients from the CI group was not statistically significant—as was the case with the difference in incidence of preeclampsia—since it is also limited by the sample size.

Analysis of the variation in the incidence of preeclampsia in high-risk patients enabled us to evaluate the effectiveness of preventive treatment based on the risk stratification applied. Thus, we observed an incidence of preeclampsia of 66.7% in the TR group compared with 9.1% in the CI group, that is, a statistically significant reduction of 57.6% in the risk of preeclampsia between the groups (Figure 3). Consequently, application of the protocol makes it possible to avoid more than half of all cases of preeclampsia in high-risk patients, consistent with the results obtained for OR and RR, which conclude that the protocol can protect against preeclampsia. Similarly, the study provided statistically significant results demonstrating that 100 mg of aspirin daily makes it possible to avoid 86% of cases of preeclampsia in the high-risk group, consistent with the tool developed by Scazzocchio et al (16). Given this reduction in incidence, we can conclude that the calculator used in the HUPHM protocol enables initiation of effective preventive treatment.

The number needed to treat was determined to evaluate effectiveness both in the overall sample (34) and in the high-risk group (1.74). These values are consistent with those obtained in previous reviews (7) and indicate that in the general low-risk population, we can avoid 1 case of preeclampsia for every 34 pregnant women treated with aspirin. This result is lower than that reported in the Cochrane meta-analysis (8). Moreover, if we focus on patients with a high risk of preeclampsia, we can conclude that we would need to treat 2 women to avoid 1 case.

We were unable to evaluate the yield of the protocol in the detection and prevention of early-onset preeclampsia, since no cases were detected in the study groups. However, our study demonstrated the reduced risk of late-onset preeclampsia both overall and in the high-risk patients. Therefore, we think that it is important to analyze the results obtained in context. On the one hand, we must consider the relevance of this condition and the potentially severe complications it can produce and that we must prevent; on the other, the material and clinical requirements of the protocol must be taken into account. It is important to consider the low cost of the drug and the absence of adverse effects in the literature (10). In addition, implementation of this type of screening in patient care workflow and obstetric follow-up was relatively simple. The tool used is based exclusively on first-trimester ultrasound values, standard analytical tests, epidemiological data, physical examination data, and the clinical history.

This approach does not require the performance of tests not previously included in the standard antenatal diagnosis or of invasive interventions or interventions that might harm the mother or fetus. Similarly, some studies show that even after screening for preeclampsia with markers not included in the standard antenatal diagnosis (such as PP13 or PlGF), this would prove efficient from a cost-utility perspective (19). The usefulness of systems similar to that implemented in HUPHM has even been proposed in centers with a low obstetric volume and no cases of preeclampsia in the sample (20). Therefore, we believe that the data are sufficiently valid for the implementation of a protocol-based strategy for prevention of preeclampsia to be considered positive.

CONCLUSIONS

Preeclampsia is a potentially severe, even fatal condition and one of the main causes of maternal and fetal morbidity and mortality. Useful tools have recently been developed for detection of the risk of preeclampsia, and the usefulness of treatment with aspirin has been demonstrated.

This study showed that the reduction in the incidence of preeclampsia in patients whose only differentiating factor was the application of a preeclampsia risk stratification

protocol based on the tool developed at HCB and subsequent treatment with 100 mg of aspirin daily in the case of high-risk patients (<1/70). Data were very positive in the high-risk group, where the risk of presenting preeclampsia decreased by 86%. Furthermore, this system was highly sensitive and specific for detecting the risk of preeclampsia, thus confirming its potential for prevention and its validity as a screening tool.

Future longitudinal studies would prove useful to ensure a greater level of statistical significance. Nevertheless, our results demonstrate the benefit of the preventive strategy followed. Therefore, we believe that the implementation of protocols such as that used at HUPHM could be recommended in all health care centers attending obstetric patients that do not yet have a preeclampsia prevention system.

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