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Predictive Capacity of Screening Methods for Preeclampsia in Early Pregnancies

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ABSTRACT

Background: Preeclampsia (PE) is a multiorgan and multifactorial disorder that occurs worldwide and is responsible for maternal mortality between 10 to 15% as a direct obstetric cause. Its early prediction would allow us to act in a timely manner to avoid possible complications.

Objective: To evaluate the predictive capacity of screening methods.

Methods: It is a prospective longitudinal study. the mean gestational age by LCC was 12.6 weeks. in which clinical risk criteria for preeclampsia (major and moderate), mean arterial pressure (MAP), uterine artery pulsatility index (IP AU), biomarkers (PIGF and PAPPA) were taken as early predictors.

Results: Of the 632 participants who met the inclusion criteria, 62 (9.8%) presented preeclampsia and 570 (90.1%) participants did not develop it. They were grouped by gestational age at delivery and the different markers were applied, obtaining them by combining them in the case of Pregnancies less than 34 weeks a prediction of 88.24% (Low PE $p \leq 0.001$ compared to High PE), in pregnancies less than 37 weeks 70% (Low PE $p \leq 0.04$ compared to High PE), in pregnancies greater than 37 weeks 68% (Low PE $p \leq 0.003$ compared to High PE).

Conclusions: The application of the different markers individually is not usually highly effective, compared to their combined application, which in our studies achieves a higher percentage of prediction, especially in early-onset preeclampsia.

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Introduction

It is essential to identify the risks and early prediction values of preeclampsia as a method of primary prevention; Likewise, it is essential to know each of them at the time of the comprehensive evaluation of the pregnant patient [1].

Nowadays, the diagnosis of early preeclampsia is associated with the simultaneous appearance of increased resistance in the blood flow of the uterine arteries and alterations in the process of angiogenesis, which, to a certain extent, can be monitored by placental markers of angiogenesis, such as Soluble FMS-like tyrosine kinase-1 (sFlt-1) and placental growth. factor (PLGF) [2,3]

Combinations of biochemical and ultrasound markers improve early prediction of preeclampsia. Screening with a combination of maternal risk factors, uterine artery Doppler, mean arterial pressure, plasma concentrations of pregnancy-related protein A, and placental growth factor, can identify about 95% of cases of early-onset preeclampsia. Interestingly, increasing research has revealed the names of some important bio-molecules that may play an important role in the vasculogenesis of early placentation [4].

The aim of this study was to evaluate the predictive capacity of preeclampsia.

Methods

The participants were taken at the Isidro Ayora Gynecological-Obstetric Hospital located in the City Center of Quito – Ecuador. It is one of the largest maternity hospitals in the city, it belongs to the public health system, considered a reference hospital (third level) Quito is the capital of Ecuador, it is located at 2850 meters high. Pregnant women who attended prenatal care at the Gineco Obstetrico Isidro Ayora hospital between 11 - 13.6 weeks of gestation from January to December 2021 were included consecutively and prospectively, a total of 632 pregnant patients who met the criteria. of inclusion of the study and who agreed to participate in order to comply with all the ethical aspects of the research. The convenience sample lasted 1 year. The research project "Predictive capacity of screening methods for preeclampsia in early pregnancies" was approved by the ethics committee of the Central University of Ecuador CEISH-UCE-Code 007-FCM-D, in addition, authorization was obtained from the Manager of the Isidro Ayora Gynecological-Obstetric Hospital to develop the research. The principles of reliability of the data obtained and

confidentiality of the patients were respected.

The participants were taken at the Hospital Gineco-Obstétrico Isidro Ayora located in the Center of the City of Quito – Ecuador. It is one of the largest maternity hospitals in the city, it belongs to the public health system, considered a reference hospital (third level).

Quito is the Capital of Ecuador, Located at an Altitude of 2850 Meters

Included consecutively and prospectively, women with difficulty attending prenatal control at the Gineco Obstétrico Isidro Ayora hospital between 11 – 13.6 weeks of pregnancy from January to June 2021, and from July to December 2022 with a total of 632 Embarrassed patients who complied with the study inclusion criteria and who agreed to participate in order to comply with all ethical aspects of the investigation. The sample was taken over 12 months in 2 stages, the first in the prenatal consultation where initial data such as clinical antecedents and risk factors were collected, in addition to the results of the uterine arteries pulsatility index as well as biomarkers, categorizing to patients at risk and not at risk, and in the second stage in the first 48 hours postpartum, identifying the presence or absence of preeclampsia. Data was collected, using a standardized questionnaire created for this purpose which contained information: age (date of birth), ethnicity, weight, height, BMI, type of birth, number of pregnancies including the current one, vaginal births, cesarean sections, abortions, gestational age, intergenesis period (last birth and gestational age) history of previous preeclampsia. They were asked about their personal history of chronic arterial hypertension, systemic lupus erythema, thrombophilia (APS), type 1, 2 or gestational diabetes, history of smoking during pregnancy, they were also asked for information on the family history of their sister or mother with preeclampsia, if they were filled in data obtained from the pulsatility index of uterine arteries, results of PAPP-A, PIGF tests, time of birth if preeclampsia is present or not, if I take ASA, dose, period of intake.

Inclusion and Exclusion Criteria

Inclusion criteria: Single pregnancy, craniocaudal length (CCL) between 45 – 84mm, complete and consistent information on clinical criteria according to NICE (major and moderate), Ultrasound findings of uterine artery pulsatility index (PI) of the uterine arteries, PAPP results -A, PIGF

Exclusion Criteria

Incomplete information, Inability to perform a Doppler study of uterine arteries, patients who did not undergo PAPP-A, PIGF, Patients with pre-existing diseases that put their lives at risk, Chromosomal anomalies or structural defects identified by ultrasound, Pregnancy loss before 24 weeks whose cause was not preeclampsia

Study Design

This prospective longitudinal study comparing tests predictive of preeclampsia.

Calculation of Gestational Age

The craniocaudal length (CCL) was taken, expressed in weeks and complete days, the same as that carried out at the time of the first trimester screening ultrasound [5].

The pulsed wave Doppler sampling port should be narrow (adjusted to approximately 2 mm) and placed on the ascending or descending branch of the uterine artery at the point closest to the internal cervical os, with an insonation angle < 30°24. To verify that the uterine artery is being examined, the maximum systolic velocity should be > 60 cm/s.; The pulsatility index is measured when at least three identical waveforms are obtained [6]. The ultrasound machine used is a General electric brand, Voluson E 10, VT20, originally from the USA.

Biomarkers (PAPPA AND PIGF) Venous blood was taken from the peripheral anticubital veins, approx. 5 cc of blood in a red cap tube without heparin [6]. The extractions were obtained between 7 and 8 in the morning in the laboratory [7].

Reventive Pharmacological Measures

Acetylsalicylic acid (ASA) 150 mg daily at night is prescribed. to patients who were identified at risk with clinical and/or ultrasound factors during 12 and 16 weeks until 36 weeks [8].

\To calculate the risk of preeclampsia and define whether there is no risk, the combinations were made using the Excel program, the risk factors were combined, clinical (1 major or 2 moderate), MAP (range over 85 mmHg), IP of uterine arteries (above the 95th percentile), PIGF (less than 14 pg) and PAPPA. (less than 0.40 Ul/ml)

Statistic Analysis

Sample calculation - We aim for a sensitivity of 95% in a cohort with a known disease prevalence of 10%. We want maximum marginal error of the estimate not to exceed 7% with a CI of 95%. So, we select Table 3B, find the row for the disease prevalence of 10%, and read the cell for the column of 95% sensitivity, which is 372. We estimate that 10% of the 372 subjects will be diseased (n = 38), and 90% will be nondiseased.

A total of 632 pregnant patients who met the study inclusion criteria and who agreed to participate in the study were included consecutively and prospectively, from January to December 2021, in order to comply with all ethical aspects of the research. The sample was of convenience and lasted 1 year.

Analysis

The analyzes were implemented in the SAS program version 9.4 and in the R program version 4.2.1, an exploratory data analysis was carried out using measures of central position and dispersion, the qualitative variables were summarized considering absolute and relative frequencies, the test was applied chi-square test to verify which of the qualitative variables are associated with preeclampsia, the diagnostic accuracy measures were estimated through sensitivity, specificity, positive predictive value and negative predictive value.

Results

Table 1 describes that of 64 participants with delivery less than 34 weeks who did not have Preeclampsia, 46 had low risk with PAM plus PI AU plus PIFG plus PAPPA more clinical markers and 18 had high risk. with markers PAM plus IP AU plus PIFG plus PAPPA more clinical markers and of the total of 17 participants with preeclampsia 2 had with markers IP AU plus PIFG low risk

and 15 had with markers PAM plus IP AU plus markers PIFG plus PAPPA plus high-risk clinicians with a P value of 0.001, meaning there was a statistically significant difference between the groups.

Table 1: Group 1 Delivery Less than 34 Weeks, Risk Association by Markers Pam Plus Ip Au Plus Pifg Plus Pappa Plus Clinical Markers And Preeclampsia.

Risk with PAM plus UAPI more PIFG more PAPPA	Preeclampsia		
	No	Yes	P-value
Low	46 (71.88%)	2 (11.76%)	0,0001
High	18 (28.13%)	15 (88.24%)	

Table 2 describes that of 44 participants with deliveries before 37 weeks, who did not have Preeclampsia, 25 had low risk with markers MAP plus IP AU plus PIFG plus PAPPA more clinical and 19 had high risk with markers PAM markers plus IP AU plus PIFG plus PAPPA more clinical and of the total of 20 participants with preeclampsia 6 had markers IP AU plus PIFG low risk and 14 (70) had markers PAM markers plus IP AU plus PIFG plus PAPPA plus high-risk clinicians with a P value of 0.04, meaning there was a statistically significant difference between the groups.

Table 2: Group 2 Delivery Before 37 Weeks Risk Association by Markers Pam Plus Pi Au Plus Pifg Plus Pappa Plus Clinical Markers and Preeclampsia.

Risk with MAP plus UAPI plus PAPPA PLUS PIGF	Preeclampsia		
	No	Yes	P-value
Low	25 (56.82%)	6 (30%)	0,04
HIgh	19 (43.18%)	14 (70%)	

Table 3 Demonstrates the Association of Factors in Pregnant Women over 37 Weeks

Of the 632 participants who were evaluated, 58 patients took acetylsalicylic acid correctly and at a dose of 150 mg, since the rest of the participants who were instructed to use it did not take it correctly, due to several reasons, the main one being that they discontinued it due to adverse effects (mainly epigastragia), the correct suboptimal dose, or they did not take it continuously, or it was intermittent, in Ecuador we had at that time only the 100 mg presentation, so some patients took 150 mg, others 100 mg, other patients began to take it after the 16th week of gestation and only 58 complied with the appropriate dosage, which is why this variable was not taken into account for the calculations, and of the 62 patients who presented preeclampsia, 4 took ASA at a dose of 150 mg. Of which 2 were in the group of less than 37 weeks and 2 in the group of more than 37 weeks.

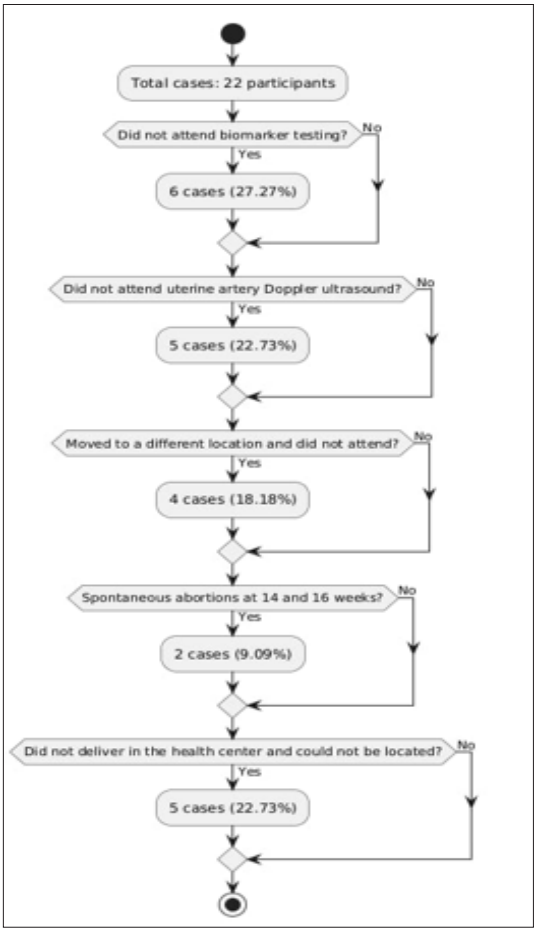
Table 3: Group 3 with Delivery Greater Than 37 Weeks, Association of Risk by Map Markers Plus Uapi Plus Pifg Plus Pappa Plus Clinical Markers and Preeclampsia.

Risk with MAP plus UAPI plus PAPPA plus PIGF	Preeclampsia		
	No	Yes	P-value
Low	310 (67.1%)	8 (32%)	0,0003
High	152 (32.9%)	17 (68%)	

Table 4: Present the Results as Means (Sd) for Parameters with Parametric Distribution and Medians (Iqr) for Non-Parametrics.

Variable	N	Mean	Std Dev	Median
Maternal age (years)	63	31.3	5.97	31.0
Intergenic period (years)	24	4.35	2.48	4.0
Weight (kg)	78	65.33	12.58	64.0
Size (cm)	63	155.54	5.79	155.0
Body mass index (BMI)	63	27.03	4.88	26.2
Craniocaudal length (mm)	32	2.26	1.10	2.0
Gestational age (weeks)	66	64.09	9.26	64.0
Gestational age by caudal skull length (cm)	37	37.53	2.63	38.3
Gestational age by craniocaudal length (cm)	12	12.68	0.61	12.5

Figure 1: Exclusion Criteria Flowchart



Discussion

In the present study, 632 women who met the inclusion criteria were analyzed. The mean age of the women in the study was 31.3 years, the mean gestational age per craniocaudal length (CCL) was 12.6 weeks. Of the total of 632 participants, 62 (9.8%) presented preeclampsia and 570 (90.1%) participants did not develop it. Of the 632 women, 81 correspond to the group that gave birth before 34 weeks. In this group, 17 (20.9%) participants presented early preeclampsia and 64 (79%) participants did not have it. Of the 632 participating women, 64 corresponded to the group that gave birth between 35 and 37 weeks, in this group 20 (31.25%) participants developed preeclampsia and 44 (68.75%) participants did not present preeclampsia. And finally, the 632 women, 487 corresponding to the group that gave birth after 37 weeks, in this group 25 (5.13%) participants presented preeclampsia and 462 (94.8%) participants did not present it. An important position regarding preeclampsia is that early-onset pre-eclampsia is associated with substantial risk of intrauterine growth restriction, whereas late-onset disease is frequently associated with maternal obesity and large-for-gestational-age neonates.

In our study, we observed prediction rates in different gestational age groups at delivery and with different markers. Thus, in our study there was a prediction with clinical criteria in pregnancies of less than 34 weeks of 41.18%; in pregnancies between 35 and 37 of 35%; pregnancies greater than 37 weeks in 36% and global preeclampsia in 37% [9-11].

In our study, we also evaluated the prediction of preeclampsia using mean arterial pressure (MAP) measurements. We obtained prediction rates in pregnancies less than 34 weeks of 58.8%, between 35 and 37 weeks of 50%, greater than 37 weeks of 28% and in global preeclampsia of 43.5% and comparatively in the study published by Matallana Katy et al, had a prediction with PAM 65% in pregnancies of less than 34 weeks, in the case of pregnancies less than 37 weeks 60% and in global preeclampsia 48% and in the study by Pedroso Marianna et al., achieved a prediction with PAM in pregnancies less than 32 weeks of 59%, in pregnancies less than 37 weeks 36% and in pregnancies greater than 37 weeks 26% [11, 12].

Furthermore, in our study, we used the uterine artery pulsatility index (IP AU) with which a prediction with IP AU was achieved in pregnancies less than 34 weeks of 64.7%, in pregnancies between 35 and 37 weeks of 55% in pregnancies greater than 37 weeks 40% and overall preeclampsia 51.6%; in the study published by Matallana Katy et al, [11]. A prediction with IP AU was achieved in pregnancies of less than 34 weeks, 70%, in pregnancies less than 37 weeks, 59%, and in global preeclampsia, 44% and in the study by Pedroso Marianna et al, achieved a prediction with IP AU less than 32 weeks 71% less than 37 weeks 47% more than 37 weeks 22% [11, 12].

In our research, detection with the PAPPA biomarker was achieved in 52.9%, in pregnancies less than 34 weeks, in pregnancies between 35 and 37 weeks 35%, in pregnancies greater than 37 weeks 40% and in global preeclampsia 41.9% and in the published study by Matallana Katy et al, A prediction with PAPPA in pregnancies less than 34 weeks was 60%, in less than 37 weeks 55% and in pregnancies greater than 37 weeks 44% while according to the study published by 10Chaemsaithong P et al, detection by PAPPA in early preeclampsia is 48.5% and 35.2 in term preeclampsia [11].

In our study there was a detection with PIGF of 70.5%, in pregnancies less than 34 weeks, between 35 and 37 weeks 60% in more than 37 weeks 48% and in global preeclampsia 58% and in the study published by Matallana Katy et al, [11]. A prediction with PIGF in less than 34 weeks was achieved by 73% in pregnancies less than 37 weeks 66% and in global preeclampsia 47% (11Matallana Katy & Olivé, 2020) while according to the study published by Chaemsaithong et al, the detection by PIGF of 60.6% and preterm preeclampsia and 34.5 in term preeclampsia [10].

Finally, in our study, a prediction was achieved in pregnancies less than 34 weeks with all the factors performed (clinical, MAP, ultrasound (IP AU), biomarkers (PAPPA and PIGF) of 86.67%, in pregnancies less than 34 weeks, in pregnancies less than 34 weeks. at 37 weeks of 70%, in pregnancies greater than 37 weeks in 68% and in global preeclampsia 74.1%

In the study by Tan et al, 2018 (13) MY, Wrighti UtA-PI, MAP and PlGF predicted 90% of early PE, (Wright, Wright, Tan, & Nicolaides, 2022) and in the study published by Matallana Katy et al. It achieved prediction with all predictive markers and in pregnancies less than 34 weeks 88%, in pregnancies less than 37 weeks 75% and in global preeclampsia 54% [11]. Screening following ACOG recommendations detects 94% of PE <32 weeks. According to the study by V Otero-Rosales MC, the UA pulsatility index combined with clinical factors and biomarkers can reach a detection rate of up to 90% in early preeclampsia [13,14].

Study Limitations

Some initial participants were lost for various reasons, including the following reasons: the first was that not all the markers were made, and the second limitation was the frequent change of residence of the study participants, followed by the fact that there were no ways to locate them. The current homes of women selected to participate in the work, and another important limitation is that the births are not carried out in reference hospitals in Quito in Ecuador, or that it is difficult to set up an adequate tracing not that is proposed or studied. The absence of diagnostic methods in countries where our study also has a limitation because it is difficult to apply to low-income populations

Conclusions

In our study when combining these clinical markers, MAP, uterine artery pulsatility index, PIGF; PAPPA we get results with values of prediction of preeclampsia, which in our studies achieves a higher percentage of prediction, especially in early-onset preeclampsia.

In developing countries such as the countries where we study we do not have the availability of these diagnostic methods for the entire population, especially in the low-income population.

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