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Diagnostic efficiency of the sFLT-1/PLGF ratio as a screening tool for preeclampsia in women with chronic hypertension

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Objective

Chronic hypertension (CH) is part of the spectrum of hypertensive disorders in pregnancy with a prevalence of 1-5%. It is considered an important risk factor for the development of preeclampsia (PE) with a risk of 10-40% to develop PE depending on the etiology of the underlying pathology and the stage of the disease. The diagnosis of PE in these women who develop an increase in blood pressure or a persistent lack of control of blood pressure accompanied or not by proteinuria is complicated. In most cases, the diagnosis of PE is confirmed late when acute complications such as renal injury, hepatic transaminase elevation or thrombocytopenia are present. In women with a pre-gestational history of chronic hypertension, diabetes mellitus or chronic kidney disease, arterial hypertension and/or proteinuria may be already existing symptoms, which complicate the differential diagnosis of PE. These conditions cause difficulties in determing a management plan in regards to follow-up and most opportune moment of delivery. An imbalance between the proangiogenic/antiangiogenic factors (sFlt-1, PlGF, sFlt-1/PlGF ratio) have been shown to be useful in various clinical scenarios of hypertension in pregnancy and placental dysfunction, however, more information is needed about the clinical usefulness of this tool (sFlt-1/PlGF ratio) in differentiating PE (screening) in women with CH who are seen in the emergency department due an increase in blood pressure.

Methods

The study was conducted at the National Institute of Perinatology in Mexico City from January 2015 to June 2017. Women more than 18 years with a singleton pregnancy and primary or secondary CH diagnosed before 20 weeks of gestation, who came to the emergency department for uncontrolled hypertension (systolic blood pressure > or equal to 140 mmHg and/or diastolic blood pressure > or equal to 90 mmHg) or additional signs of PE (headache, scotomas, blurred vision, seizures of any kind, epigastralgia, edema) were included. Women with thrombophilia were excluded. The purpose of the study was explained to all the patients and the patients gave their written informed consent. At time of inclusion, vital signs were assessed, and maternal age, gestational age, parity, weight, height, antihypertensive treatment taken documented. The initial evaluation included: fetal well-being evaluated with non stress test, determinations of hemoglobin, hematocrit, platelet count, alanine amino and aspartate transferase levels, creatinine, protein/creatinine ratio in a random urine sample, as well as determination of proteins and creatinine clearance in urine of 24 hrs, in addition to this 5 ml of peripheral blood was taken to measure serum concentrations of sFlt-1, PLGF with an automatic KRYPTOR compact Plus equipment, BRAHMS-Instruments and were results were reported in ng/ml. The ratio sFlt1/PLGF was obtained by simple division of the two values. The PE diagnosis was established in the emergency department following the ACOG recommendations (American College of Obstetricians and Gynecologists 2013). To perform the definitive diagnosis, uncontrolled CH was considered in women with a history of CH who did not fulfill any PE criteria. Women with indication for immediate delivery were admitted to the labor area after stabilizing vital signs and the decision between a normal delivery or a cesarean section was made according to obstetric criteria. Patients without indication for immediate delivery were transferred to the hospitalization area for monitoring and surveillance: including blood pressure measurement twice per day, diuresis, laboratory tests and monitoring of fetal well-being every 72 hours following the institutional protocol. In the cases of PE with severity criteria, the decision to establish an expectant management and a fetal lung maturity scheme was determined in conjunction with the obstetrics department. All cases of PE in women with CH were kept in hospital until the woman had delivered. Women who did not develop PE and showed normal vital signs were discharged from hospital and continued monitoring by external consultation with home blood pressure monitoring and once a week they underwent laboratory tests. Three groups were formed for analysis, Group A: women with CH with PE, Group B:

women with uncontrolled CH who did not meet any PE criteria, Group C: a control group of healthy women matched with women with PE by gestational age. The follow-up was performed in all cases 12 weeks after the birth, to confirm that the laboratory alterations and clinical signs had resolved and by that establish the diagnosis of PE or CH. The statistical analysis was carried out using the SPSS version 22 software. The comparison between groups was performed using the U Mann-Whitney test and the comparison between the 3 groups was performed with Kruskal-Wallis with Bonferroni correction. Statistical signifance was considered for p<0. 05. The predictive performance was evaluated with receiver operating characteristic curve.

Results

We included 67 women in the analysis; 30 with CH and diagnosis of PE (group A), 12 with uncontrolled CH without PE (Group B) and a control group of 25 healthy women (Group C). The general population characteristics showed differences between the three groups in systolic blood pressure, diastolic blood pressure, urea, creatinine and platelet levels at the time of inclusion. If only groups A and B were analyzed considering the variables necessary to make the diagnosis of PE, no differences were found between the groups (age, body mass index, weeks of gestation at the time of inclusion, systolic blood pressure, diastolic blood pressure, aspartate amino transferase, alanine transaminase, urea, creatinine, uric acid, total bilirubin, platelets, creatinine clearance, protein in 24 hours urine). The sFlt-1/PlGF ratio at the time of admission to the emergency department was higher in women with PE compared to uncontrolled CH patients (215. 5 versus 9. 65, p <0. 001). The ratio was also higher in these 2 groups compared to healthy women (group C) (3. 66, p <0. 001). In the comparison between group A and B the concentration of sFlt-1 was higher in group A (7564 versus 1281 ng / ml, p <0. 001) whereas PLGF was lower (34. 39 versus 169 ng / ml, p <0. 001) and the ratio was higher in group A (215. 5 vs 9. 65 p <0. 001) An ROC was performed with the sFlt-1/PLGF ratio and the final diagnosis, provided an area under the curve of 1 in the diagnosis of preeclampsia in patients with CH, different cut-off points of the ratio sFlt-1 / PLGF (20, 23, 30, 45) were evaluated and they all showed a detection rate of 100%.

Conclusion

Our results show a statistically significant difference in the sFLT-1/PLGF ratio between women with PE and those with uncontrolled CH, as well as in the individual determinations of sFlt-1 and PlGF between these groups. We obtained an area under the curve of 1, which indicates that the ratio has a high diagnostic yield in women with suspected PE and CH. Different cut-off points of the ratio 20, 23, 30, 45 were analyzed showing a detection rate of 100% and specificities greater than 99%. When the classic criteria for the diagnosis of PE were analyzed, no differences were found between group A and group B, which shows that they are not useful to rule out the diagnosis of PE in patients with CH. The study shows that the measurement of the sFlt-1/PLGF ratio has a good diagnostic performance when used in women with CH with clinical suspicion of PE and is an excellent tool to be used in the emergency department to perform the differential diagnosis between PE and uncontrolled CH. Although the sFlt-1 / PLGF ratio does not substitute medical criteria or management, its determination can contribute to establish the management plan, to decide the time of hospital surveillance, the frequency and extension of laboratory and the time of termination of pregnancy, in this way the prevalence of premature iatogenic births would be reduced, also reducing morbidity and perinatal mortality.