Pregnancy Hypertension 17 (2019) 64–68

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

External validation of the Fetal Medicine Foundation algorithm for the prediction of preeclampsia in a Brazilian population

Karina Bilda de Castro Rezende[a,b,c,*], Antônio José Ledo Alves da Cunha[c,d], Joffre Amim Junior[a,b,c], Rita Guérios Bornia[a,b,c]

[a] Maternidade Escola da Universidade Federal do Rio de Janeiro, Brazil
[b] Professional Masters Program of Perinatal Health, Brazil
[c] Faculdade de Medicina da, Universidade Federal do Rio de Janeiro, Brazil
[d] Laboratório Multidisciplinar de Epidemiologia e Saúde-LAMPES, UFRJ, Brazil

ARTICLE INFO

Keywords:
Preeclampsia
Mass screening
External validation
Reproducibility of results
Clinical prediction model

1. Introduction

Preeclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality [1], affecting 2–8% of pregnancies [2,3]. Despite knowledge of numerous risk factors, only about 35% of all cases of PE and 40% of preterm cases are predicted [4,5]. The value of PE screening lies in the ability to implement prophylactic use of low-dose aspirin in a timely manner in cases identified as high risk. A significant benefit in terms of reducing the relative risk of PE has been observed when low-dose aspirin is started at or before 16 weeks of gestation in high-risk pregnancies [6–8].

PE screening that incorporates and combines maternal history data with biophysical and/or biochemical markers is the most promising approach for early prediction, with considerably wide variation in detection rates (range, 46–99%) [9–15]. Factors that may explain this variation include differences in the profiles of study populations and limited external validation of algorithms used in screening [16]. External validation, which evaluates the accuracy of predictive models in patients from different populations to enable generalisation, is essential before such models are implemented in clinical practice [17,18].

The Fetal Medicine Foundation (FMF) freely provides to certified doctors a constantly updated predictive model that estimates PE risk according to gestational age (GA) at delivery. Despite the availability of an updated predictive model [14,15], its coefficients are not yet included in the free version of the FMF First Trimester Screening Program. This programme uses coefficients from Wright et al. [13] to calculate the risk of PE, and produce single reports on maternal factors, first-trimester scan data, the mean uterine artery pulsatility index (UtAPI), mean arterial blood pressure (MAP), and risks of major obstetrics syndromes, including PE. The aim of this study was to validate the FMF algorithm (FMF2012) for PE using maternal risk factors, MAP, and the UtAPI in a Brazilian population.

Methods

The data for this observational cohort study were derived from the application of the FMF algorithm in all singleton pregnant women undergoing routine first-trimester screening at 11 + 0 to 13 + 6 weeks of gestation between October 2010 and December 2015. The study was conducted at the Maternidade Escola da Universidade Federal do Rio de Janeiro, a non-profit university hospital that serves exclusively patients from the public health system, and receives undergraduate and postgraduate students in the health care sector. According to the hospital health care indicators, about 37% of the pregnant women were in the first trimester of pregnancy, of which 72% underwent first screening screening [19].

This study was part of a larger ongoing study examining the performance of the FMF2012 algorithm. Maternal characteristics of the study population have been described in detail previously [20]. The local ethics committee approved the study protocol (CAAE 25575913.2.0000.5275) and all patients provided written informed

* Corresponding author at: Maternidade Escola da Universidade Federal do Rio de Janeiro, Rua das Laranjeiras, 180 – Laranjeiras, Rio de Janeiro, RJ CEP 22240-000, Brazil.
E-mail address: karina@me.ufrj.br (K.B.d.C. Rezende).

https://doi.org/10.1016/j.preghy.2019.05.006
Received 5 December 2018; Received in revised form 18 February 2019; Accepted 8 May 2019
Available online 10 May 2019

consent.

Sample size estimation was based on the hospital PE prevalence of 6.74% [3], an α error of 5%, and a statistical power of 95%. The results indicated that a sample of at least 852 pregnant women, with 48 cases of PE and 804 normal cases, was required. However, we considered all singleton pregnancies with first-trimester screening for PE involving examination of maternal factors and biophysical markers using the FMF algorithm during the study period to be eligible for study inclusion. The following exclusion criteria applied were the same described by FMF: pregnancy with chromosomal and/or structural abnormality, miscarriage or fetal death before 24 weeks of gestation, use of acetylsalicylic acid (ASA) during pregnancy before 16 weeks of gestation, and delivery of a small-for-gestational-age (SGA) new-born to a mother without PE.

Patients were scheduled for first-trimester screening at 11 + 0 to 13 + 6 weeks of gestation. This examination included recording of maternal characteristics, measurement of fetal crown–rump length (CRL), measurement of right and left UtAPIs by transabdominal colour Doppler ultrasound (Nemio, Toshiba, Tokyo, Japan; Xario, Toshiba, Tokyo, Japan; Medison V10, Medison, Seoul, South Korea or Aloka, Aloka Co., Tokyo, Japan) by six certified doctors, and measurement of MAP with an automated device (3BTO-A2, Microlife, Taipei, Taiwan or ONROM, OMRON Corporation, Kyoto, Japan) using a standardised method (in both arms simultaneously while the mother was sitting after ≥10 min rest) [20]. All data were entered into the FMF2012 software.

The maternal factors included in this study were the maternal history and characteristics included in the FMF2012 algorithm, obtained *via* a patient questionnaire administered by a medical doctor. Continuous variables were maternal age (in years), weight (in kilograms), and height (in centimetres). Categorical variables were self-reported ethnicity (black, white, or mixed), parity (nulliparous, parous with no previous PE, or parous with previous PE), maternal family history of PE (yes or no), smoking during pregnancy (yes or no), history of previous hypertension (yes or no), diabetes type I (yes or no), diabetes type II (yes or no), systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS; yes or no), and use of assisted reproductive technology (ART; yes or no).

The biophysical markers considered in this study were CRL (in millimetres); MAP [in mmHg and multiples of median (MoM)] [21], and mean UtAPI (arithmetic mean, in MoM) [22]. The FMF2012 algorithm calculated MoM values using an MoM equation [13].

Risk scores were calculated according to the competitive risk model described by Wright et al. [13] from maternal characteristics and biomarkers (MAP and UtAPI), and were presented as the risk of PE development before 34, 37, and 42 weeks. Cut-off values for positivity for these three timepoints were 1/200, 1/57, and 1/12, respectively [23].

The screening results did not interfere in professional conduct during prenatal care. As FMF algorithm was not validated in our hospital, ASA prescription for PE prophylaxis was based on WHO recommendations [24,25].

Data on pregnancy outcomes (PE occurrence and GA at delivery) were collected from hospital records. PE was defined according to the International Society for the Study of Hypertension in Pregnancy as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg at least twice with 4 h of difference after 20 weeks of gestation with proteinuria (≥300 mg in 24-h urine). In patients with chronic hypertension, PE was defined as the appearance of proteinuria (≥300 mg in 24-h urine) after 20 weeks of gestation [26].

Women were grouped according to the presence of PE. Cases of PE were classified according to GA at delivery: PE < 34 or early PE (delivery occurring before 34 weeks of gestation), PE < 37 or preterm PE (delivery occurring before 37 weeks of gestation), and PE < 42 or total PE (including all cases of PE) [23]. GA at birth was calculated based on the last menstrual period or first-trimester ultrasound screening. When the difference between these timepoints was > 7 days, the ultrasound estimation was used.

1.1. Statistical analysis

The STATA 13 statistical software package (StatCorp, College Station, TX, USA) was used for data analyses. The medians of continuous variables and ratios of categorical variables were compared between outcome groups using the Mann–Whitney *U* test and the chi-squared test or Fisher's test (when the expected value was < 5), respectively. Differences between groups were considered to be significant when *p*-values were < 0.05.

Age, weight, and height values were centred by subtracting the observed mean from each maternal measured value. UtAPI and MAP values were log10 transformed to obtain normal distribution. Their respective MoM values were presented numerically as medians with 95% confidence intervals (CIs) and compared according to the 95% CI limits in the normal and PE (PE < 34, PE < 37, and PE < 42) groups.

Linear regression analyses were performed to verify the correlation of log10 UtAPI and log10MAP values with GA at birth in the PE and non-PE groups, as performed by Wright et al. [13] when validating the model. Residues were analysed to check the adequacy of the observed values according to the estimates represented by the regression line. The performance of screening for total, preterm, and early PE was determined by calculating sensitivity and specificity, positive predictive values (PPVs), negative predictive values (NPVs), and positive likelihood ratios (LR + s), and by performing receiver operating characteristic (ROC) curve analysis.

2. Results

First-trimester screening was carried out in 1934 singleton pregnancies. We excluded 403 cases due to fetal aneuploidies (n = 7); major fetal malformation (n = 28); miscarriage, termination, or fetal death before 24 weeks of gestation (n = 18); ASA use at ≤ 16 weeks of gestation (n = 103); SGA neonatal status in the absence of PE (n = 69); and missing outcome data (n = 178). The remaining 1531 cases were included in the study. The sample included 120 (7.8%) cases of PE, of which 26 (1.7%) were PE < 37 and 11 (0.65%) were PE < 34. Mean maternal weight, height, and age were 67 kg, 160 cm, and 27 years, respectively. According to the determined cut-off values, 15% of our final sample was classified as at high risk of PE development.

The characteristics of the study population are presented in Table 1. PE rates in this sample did not differ according to ethnicity, smoking, or family history of PE, or according to ART use, although our sample contained few cases of the latter, preventing meaningful inference. In addition, our sample contained no case of SLE or APS.

Median UtAPI values were significantly higher in the early and preterm PE groups than in the normal group, despite the small number of pathological cases in our sample. This difference did not appear between the total PE and normal groups. MAP values did not differ significantly among the early and preterm PE groups and the normal group, but were considerably higher in the total PE group compared with the normal group (Table 2).

Table 3 presents regression model data, and Fig. 1 shows estimated regression lines. The regression analysis of biophysical markers showed a significant inverse correlation between UtAPI MoM values and GA at birth in pregnancies that evolved with PE. No such correlation was found between MAP values and GA at birth in cases that evolved with PE.

PE screening performance results were as follows: for PE < 34, sensitivity 63.3% (95% CI 29.74–97.53%), specificity 86.1% (95% CI 84.37–87.85%), LR + 4.58, PPV 3.22%, and NPV 99.72%; for PE < 37, sensitivity 46.1% (95% CI 25.61–66.68%), specificity 86.1% (95% CI 84.43–87.92%), LR + 3.33, PPV 5.40%, and NPV 98.90%; and for PE < 42, sensitivity 33.3% (95% CI 24.77–41.89%), specificity 85.8% (95% CI 84.00–87.64%), LR + 2.40, PPV 16.49%, and NPV 93.70%.

With a 10% fixed false-positive rate, the area under the ROC curve (AUC) for total PE was 0.7155 (95% CI 0.66–0.76), with a sensitivity of 26.67%. For PE < 37, the AUC was 0.77 (95% CI 0.68–0.86), with

Table 1
Maternal characteristics in the study groups.

Characteristic	Normal (n = 1411)	PE (n = 120)	p^*
Maternal age (median, years)	27 [22–32]	30 [24–35]	0.01
Maternal weight (median, kg)	64.5 [56.9–74.3]	73.55 [61.47–86.57]	0.000
Maternal height (median, cm)	160 [156–165]	161 [157–165]	0.92
CRL (median, mm)	63.9 [58–70]	62 [55–70]	0.21
Ethnicity			
White	548 (61.2)	41 (34.1)	0.313
Black	269 (19.06)	27 (22.5)	0.360
Mixed	593 (42.02)	52 (43.3)	0.781
Parity			
Nulliparous	772 (54.7)	68 (56.6)	0.680
Parous with no previous PE	604 (42.8)	43 (35.8)	0.000
Parous with previous PE	35 (2.48)	9 (7.5)	0.002
Smoking	54 (3.82)	4 (3.33)	0.786
Family (maternal) history of PE	83 (5.88)	10 (8.33)	0.281
Assisted conception	2 (0.14)	1 (0.8)	0.100
HAC	33 (2.33)	15 (12.5)	0.000
Type I diabetes mellitus	11 (0.77)	4 (3.33)	0.006
Type II diabetes mellitus	15 (1.0)	4 (3.33)	0.031
SLE or APS	0	0	
GA at birth (weeks)	39.43 [38.57–40.29]	38.29 [37.43–39.29]	0.000

Values in parentheses are proportions and those in brackets are interquartile ranges. PE, preeclampsia; CRL, crown–rump length; HAC, chronic hypertension; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; GA, gestational age.

* Chi-squared or Fisher's exact test for categorical variables, Mann–Whitney test for continuous variables.

sensitivity of 38%. For PE < 34, the AUC was 0.84 (95% CI 0.71–0.97), with a sensitivity of 54% (Fig. 2).

3. Discussion

This study presents the results of the application of the FMF2012 predictive model for PE according to GA at delivery in a Brazilian population. The AUCs obtained in this study demonstrate the good discriminatory ability of the screening test for PE < 34, PE < 37, and total PE, as the lower limits of the 95% CIs were > 0.5, mainly at the expense of high specificity. We had few cases of PE < 34 and PE < 37, reflected in the 95% CIs of the AUCs and sensitivity for these groups.

The PE prevalence of 7.5% was three times that reported in other screening studies [10,11,23,27,28]. Moreover, 15% of our final sample was classified as high risk, which was higher than the 10% reported by Akolekar et al. [23]. We have already observed [20] that the coefficients of FMF2012 model are under or overestimated in our population. This result suggests that risk factors other than those included as predictive factors in the FMF2012 could be associated with PE risk in our population and may compromise PE screening.

The inverse correlation between UtAPI MoM values and GA at birth in pregnancies that evolved with PE in our study was similar to the findings for the FMF2012 algorithm reference population [13]. However, the correlation between MAP MoM values and GA at birth was not significant, unlike observed in the reference model [13]. The MoM values included in the regression analysis were generated by the algorithm, with significant contributions of maternal ethnicity and weight. Pregnant women with high MAP at the time of screening are more likely to have chronic hypertension and usually do not exceed 40 weeks of gestation, mainly in severe forms and in cases with maternal and/or fetal complications, when delivery at an earlier GA is indicated [28]. Poon et al. [29] also reported that MAP MoM values in the first trimester of pregnancy did not differ significantly according to GA at delivery. Cnossen et al. [28] and Scazzocchio et al. [30] reported similar findings. We chose to present absolute and MoM values for biophysical markers; the FMF2012 algorithm uses MoM values in predictive models, but absolute values are interpreted more easily by clinicians.

Table 3
Regression model results for $\log_{10}$ biomarker values in pregnancies with and without preeclampsia.

Pregnancy	Marker	Intercept	SD	p	β	SD	p
PE	UtAPI	0.43290	0.1696	0.012	−0.01107	0.004495	0.015
	MAP	0.06526	0.0556	0.243	−0.00125	0.001479	0.395
NORMAL	UtAPI	0.19139	0.0828	0.817	0.00066	0.002107	0.752
	MAP	0.05561	0.0239	0.020	−0.00128	0.000609	0.012

SD, standard deviation; PE, preeclampsia; UtAPI, uterine artery pulsatility index; MAP, mean arterial pressure.

Predictive models for PE, whether developed in British [13–15] or other [10] populations, have received criticism because PPVs are low, around 7% [31,32], despite the detection rates and AUCs reported in FMF studies are high [13,14,23,33]. Low PPVs reflect the low prevalence of the event of interest in the populations studied, and not the test performance. In populations with higher prevalence of PE, such as ours, tests with high sensitivity should have higher PPVs, even with a number of false-positive cases. Preterm forms of PE, which benefit most from preventive measures, are less frequent than late forms in any population, so screening tests are unlikely to have high PPVs. As PE is associated to serious maternal and fetal consequences, good predictive tests that have good sensitivity and PPV values would be required for incorporation in clinical practice.

Our results show that in screening for PE in the first trimester using maternal factors, the MAP and UtAPI are inversely related to GA at delivery, as described by Wright et al. [13]. Because of the high cost of biochemical marker analysis in Brazil, such analysis cannot be added to universal screening, despite its ability to improve screening performance.

The limitations of our study are related mainly to the small number of cases of clinical preterm PE, which would improve the performance of predictive models and are the main targets of the prevention strategy. In addition, formal incorporation of the 2013 ASA protocol [24,25,34,35] as a preventive strategy for pregnancies classified as high risk led us to exclude 103 (5.5%) potentially true-positive cases from the sample. This exclusion may have compromised the overall performance of the test. As doing nothing for pregnancies with high risk for PE is no longer an option, this strategy reinforces our commitment to quality assurance, even frustrating our validation study in progress. We did not have access to previous medical records for confirmation of data

Table 2
Biophysical marker values.

Marker	PE < 34	PE < 37	Total PE	Normal
UtAPI	2.29 (1.86–2.71)	2.15 (1.88–2.45)	1.75 (1.55–1.90)	1.72 (1.68–1.75)
UtAPI MoM	1.38 (1.15–1.61)	1.29 (1.16 –1.48)	1.11 (0.96–1.2)	1.06 (1.05–1.07)
MAP	90.8 (82.0–101.01)	91.45 (85.07–94.64)	90.05 (88.45–91.67)	83.8 (83.2–84.38)
MAP MoM	1.08 (0.94–1.20)	1.06 (1.0–1.08)	1.04 (1.01–1.06)	0.99 (0.98–0.99)

PE < 34, early preeclampsia; PE < 37, preterm preeclampsia; PE, preeclampsia; UtAPI, uterine artery pulsatility index; MoM, multiple of median; MAP, mean arterial pressure. Values are presented as median (95% confidence interval).

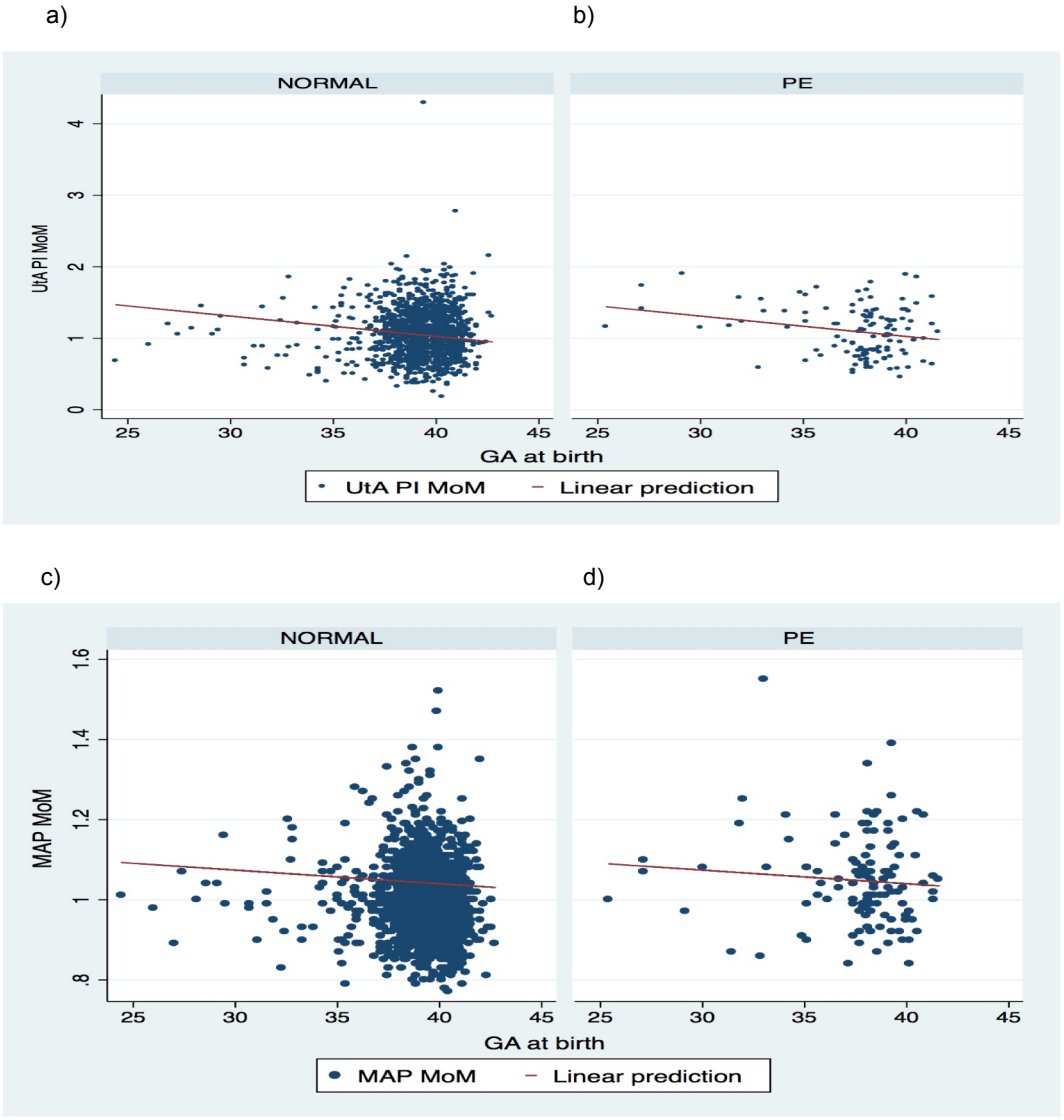

Fig. 1. Scatter diagrams and regression lines for the relationships of multiple of median (MoM) values for (a, b) the uterine artery pulsatility index (UtAPI) and (c, d) mean arterial pressure (MAP) with gestational age (GA) at delivery. PE, preeclampsia.

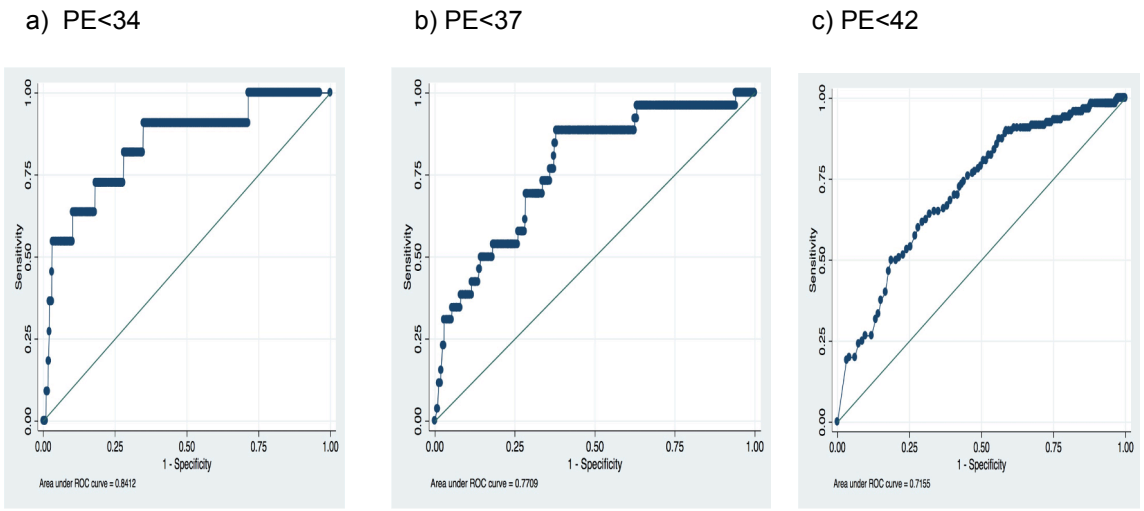

Fig. 2. Receiver operating characteristic (ROC) curves for the prediction of preeclampsia (PE) development before (a) 34, (b) 37, and (c) 42 gestational weeks.

on family history of PE, except in a few cases in which previous pregnancies were monitored in our unit. We believe that the accuracy of participants' responses about the family history of PE was likely low due to memory bias. However, our results reflect the reality of daily practice [19].

The strength of this study is the homogeneity of methodology regarding CCN, UtAPI, and MAP measurements and interviews, with consistency in data collection as recommended by the FMF. This aspect of the study reinforces the feasibility of routine screening following standardised protocols. We also observed that the trends of biophysical markers, which are operator dependent, in our sample were similar to those in the reference model [13].

This external validation of the FMF2012 algorithm demonstrated good performance of the test in ruling out the risk of PE development, but unsatisfactory performance in identifying cases in which PE developed. The exclusion of high-risk cases with ASA use probably compromised model performance in this sample. The lack of generalisability of the FMF2012 predictive model for PE observed in our sample supports the conclusion that different scenarios undermine the original positive performance obtained in the reference population. Given the conditions of real practical life, there are no acceptable medical reasons to apply the algorithm for detecting preeclampsia as a routine in our patients, except in research scenarios.

Funding

Authors thank Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro [E-26/110.578/2012].

Declaration of Competing Interest

No potential conflict of interest was reported by the authors.

References

[1] World Health Organization. Make every mother and child count. World Health Rep. Geneva: WHO; 2005.[Internet]. [cited 2016 Nov 29]. Available from: http://www.who.int/whr/2005/whr2005_en.pdf.
[2] L. Duley, Pre-eclampsia and the hypertensive disorders of pregnancy, Br. Med. Bull. 67 (2003) 161–176.
[3] K.B.d.C. Rezende, R.G. Bornia, A.P.V.d.S. Esteves, et al., Preeclampsia: prevalence and perinatal repercussions in a University Hospital in Rio de Janeiro, Brazil, Pregnancy Hypertens. 6 (2016) 253–255.
[4] L.C.Y. Poon, N.A. Kametas, T. Chelemen, et al., Maternal risk factors for hypertensive disorders in pregnancy: a multivariate approach, J. Hum. Hypertens. 24 (2010) 104–110.
[5] National Collaborating Center for Women's and Children's Health (UK), Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy, Royal College of Obstetricians and Gynaecologists Press, London, 2010.
[6] E. Bujold, S. Roberge, Y. Lacasse, et al., Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis, Obstet Gynecol. 116 (2010) 402–414.
[7] D.L. Rolnik, D. Wright, L.C. Poon, et al., Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia, N. Engl. J. Med. 377 (2017) 613–622.
[8] S. Roberge, E. Bujold, K.H. Nicolaides, Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis, Am. J. Obstet. Gynecol. 218 (287–293) (2018).
[9] F. Audibert, I. Boucoiran, N. An, et al., Screening for preeclampsia using first-trimester serum markers and uterine artery Doppler in nulliparous women, Am. J. Obstet. Gynecol. 203 (2010) 383.e1–383.e8.
[10] J. Caradeux, R. Serra, J.K. Nien, et al., First trimester prediction of early onset preeclampsia using demographic, clinical, and sonographic data: a cohort study, Prenat. Diagn. 33 (2013) 732–736.
[11] A.A. Baschat, L.S. Magder, L.E. Doyle, et al., Prediction of preeclampsia utilizing the first trimester screening examination, Am. J. Obstet. Gynecol. 211 (2014) 514.e1–514.e7.
[12] The Fetal Medicine Foundation.[Homepage]. [accessed on 2018 jun.06] Available from: https://courses.fetalmedicine.com/user/get_license/.
[13] D. Wright, R. Akolekar, A. Syngelaki, et al., A competing risks model in early screening for preeclampsia, Fetal DiagnTher. 32 (2012) 171–178.
[14] D. Wright, A. Syngelaki, R. Akolekar, L.C. Poon, K.H. Nicolaides, Competing risks model in screening for preeclampsia by maternal characteristicsand medical history, Am. J. Obstet. Gynecol. 213 (2015) 62.e1–62.e10.
[15] N. O'Gorman, D. Wright, A. Syngelaki, R. Akolekar, A. Wright, L.C. Poon, K.H. Nicolaides, Competingrisksmodel in screening for preeclampsiaby maternal factorsandbiomarkersat 11–13 weeksgestation, Am. J. Obstet. Gynecol. 214 (2016) 103.e1–103.e12.
[16] D.G. Altman, Y. Vergouwe, P. Royston, et al., Prognosis and prognostic research: validating a prognostic model, BMJ 338 (2009) b.
[17] A.C. Justice, K.E. Covinsky, J.A. Berlin, Assessing the generalizability of prognostic information, Ann. Intern. Med. 130 (1999) 515–524.
[18] S.E. Bleekera, H.A. Molla, E.W. Steyerbergd, A.R.T. Dondersb, G. Derksen-Lubsenc, D.E. Grobbeeb, K.G.M. Moonsb, External validation is necessary in prediction research: a clinical example, J. Clin. Epidemol. 56 (2006) 826–832. Available from: https://www.jclinepi.com/article/S0895-4356(03)00207-5/pdf.
[19] Maternidade Escola, Universidade Federal do Rio de Janeiro. Relatório divisão adjunta de atenção à saúde: indicadores assistências, 2011. [Accessed on December 29th, 2017]. Available in: http://www.maternidade.ufrj.br/portal/index.php/atencaoasaude/indicadores-asssistenciais.
[20] K.B.C. Rezende, A.J.L.A. Cunha, C. Pritsivelis, E.C. Faleiro, J. Amim Junior, R.G. Bornia, How do maternal factors impact preeclampsia prediction in Brazilian population? J. Maternal-Fetal Neonatal Med. (2017), https://doi.org/10.1080/14767058.2017.1399115 Available from: https://www.tandfonline.com/doi/abs/10.1080/14767058.2017.1399115.
[21] A. Tayyar, K. Krithinakis, A. Wright, D. Wright, K.H. Nicolaides, Mean arterial pressure at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia, Ultrasound Obstet. Gynecol. 47 (2016) 573–579.
[22] W. Plasencia, N. Maiz, S. Bonino, C. Kaihura, K.H. Nicolaides, Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia, Ultrasound Obstet. Gynecol. 30 (2007) 742–749.
[23] R. Akolekar, A. Syngelaki, L. Poon, et al., Competing risks model in early screening for by biophysical and biochemical markers, Fetal Diagn. Ther. 33 (2013) 8–15.
[24] World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia, 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241548335_eng.pdf.
[25] R.G. Bornia, I.B. Costa Junior, Junior J. Amim, Protocolos assistenciais: Maternidade Escola Universidade Federal do Rio de Janeiro, POD, Rio de Janeiro, 2013.
[26] M.A. Brown, M.D. Lindheimer, M. De Swiet, et al., The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of hypertension in Pregnancy(ISSHP), Hypertens. Pregnancy. 20 (2001) IX–XIV.
[27] F.J. Park, C.H. Leung, L.C. Poon, P.F. Williams, S.J. Rothwell, J.A. Hyett, Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy, Aust. NZJ Obstet. Gynaecol. 53 (6) (2013) 532–539. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23919594.
[28] E. Scazzocchio, F. Crovetto, S. Triunfo, E. Gratacós, F. Figueras, Validation of a first-trimester screening model for preeclampsia in an unselected population, Obstetrics, Gynecol. Reprod. Med. Depar. 49 (2017) 188–193. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27257033.
[29] L.C. Poon, N.A. Kametas, I. Pandeva, C. Valência, K.H. Nicolaides, Mean arterial pressure at 11 + 0 to 13 + 6 weeks in the prediction of preeclampsia, Hypertension 51 (4) (2008) 1027–1033.
[30] J.S. Cnossen, R.K. Morris, G. Riet, W.J.M. Ben, J.A.M. Van Der Post, A. Coomarasamy, et al., Use of uterine artery doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis, CMAJ 178 (6) (2008) 701–711.
[31] A.A. Baschat, First-trimester screening for pre-eclampsia: moving from personalized risk prediction to prevention, Ultrasound Obstet. Gynecol. 45 (2) (2015) 119–129. Available from: https://www.hvra.com/sites/hvra/files/baschat-2015-ltrasound_in_obstetrics_gynecology.pdf.
[32] American College Of Obstetricians And Gynecologists, ACOG Committee Opinion, n.638. First-trimester risk assessment for early-onset preeclampsia, Obstet. Gynecol. 126 (3) (2015) e25–e27.
[33] R. Akolekar, A. Syngelaki, R. Sarquis, et al., Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11–13 weeks, Prenat. Diagn. 31 (2011) 66–74.
[34] L.C. Poon, D.L. Rolnik, M.Y. Tan, J.L. Delgado, T. Tsokaki, R. Akolekar, et al., ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm, Ultrasound Obstet. Gynecol. 51 (2018) 738–742.
[35] National Collaborating Centre for Women's and Children's Health (UK), Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy, Royal College of Obstetricians and Gynaecologists Press, London, 2010.