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Original Article

Taiwanese new direction in prediction of early pregnancy preeclampsia

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ABSTRACT

Objective: First trimester screening is essential to preeclampsia (PE) prevention. Fetal Medicine Foundation (FMF) model combined maternal characteristics with mean arterial pressure (MAP), uterine artery pulsatility index (UtAPI) and placental growth factor (PlGF) to estimate risk. High detection rate (DR) was observed in Asia. The study aims to evaluate performance of screening in Taiwan.

Materials and methods: This was a prospective and non-interventional study between January, 2017 and June, 2018. Data was collected from 700 pregnant women at 11^{+0}–13^{+6} gestational week. Maternal characteristics were recorded. MAP, UtAPI and PlGF were measured and converted into Multiple of the Median (MoM). Patient-specific risks were calculated with FMF model. Performance of screening was examined by ROC curve and DR.

Results: 25 women (3.57%) contracted PE, including 8 with preterm PE (1.14%). In preterm PE, mean MoM of MAP and UtAPI were higher (1.096 vs 1.000; 1.084 vs 1.035). Mean MoM of PlGF was lower (0.927 vs 1.031). DR in preterm PE achieved 12.5%, 50.0%, 50.0% and 62.5% at false-positive rate (FPR) of 5%, 10%, 15% and 20%.

Conclusion: FMF model showed high DR for PE in Taiwan. Integration of PE and Down screening could set up a one-step workflow.

Introduction

Preeclampsia (PE) affects about 1–2% pregnancies in Taiwan [1]. This hypertensive syndrome that occurs during pregnancy results in real risk of maternal and perinatal health [2]. The negative impact on mother and fetus is more hazardous in preterm PE (delivery ≤37th week of gestation) [3]. To avoid preterm delivery and its complications, adequate prevention in early gestation is needed [4]. Aspirin for Evidence-Based Preeclampsia Prevention trial (ASPRE) demonstrated that low-dose Aspirin (150 mg/day) significantly reduced the incidence (50%) of PE in high-risk women [5]. Moreover, a systematic review and meta-analysis reported that prophylactic use of Aspirin (100 mg/day) at <16th week of gestation substantially lessened the risk (65%) of preterm PE [6]. Consequently, early identification of high risk of PE is essential to proper prevention.

Traditional screening for PE is based on maternal characteristic and medical history defined by professional associations. The National Institute for Health and Care Excellence (NICE) recommends women with one high-risk factor or two moderate-risk factors take Aspirin (75 mg/day) at 12th week of gestation [7]. The American College of Obstetricians and Gynecologists (ACOG) recommends women with one high factor or two moderate factors take Aspirin (81 mg/day) at 12th–28th week of gestation [8]. However, both models showed insufficient power for PE screening in a recent research [9]. Extensive studies were dedicated to identifying promising biomarkers to predict PE at 11^{+0}–13^{+6} week of gestation. Mean arterial pressure (MAP), uterine artery pulsatility index (UtAPI) and placental growth factor (PlGF) appeared to be the most

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powerful for first trimester screening [10]. As a result, a novel model (FMF triple test) developed by FMF combined maternal characteristics with biophysical and biochemical factors to estimate patient-specific risk based on Bayes theorem [11]. A recent study in Asian population showed the performance of FMF triple test is superior to those of NICE and ACOG [12]. The objective of this study is to evaluate the performance of FMF triple test and set up a standard protocol for first trimester screening of PE in Taiwan.

Materials and methods

This was a prospective, single-center and non-interventional cohort study between January 1st, 2017 and June 30th, 2018 at Taipei Chang Gung Memorial Hospital in Taiwan. Data was derived from routine examination of 700 women with singleton pregnancies at 11^{+0}–13^{+6} week of gestation. Written informed consent was obtained from all eligible women for participation. This study was approved by Chang Gung Medical Foundation Institutional Review Board (CGMF Ref. No. 201601672B0 and No. 103–5484B).

Participants

Inclusion criteria were ≥18 years old women with singleton pregnancy at 11^{+0}–13^{+6} week of gestation undergoing first-trimester screening and subsequently delivering a live birth or stillbirth at ≥24th week of gestation. Gestational age was measured with fetal crown-rump length [13]. Pregnancies with maternal factors, such as mental and severe illness, or fetal abnormality diagnosed at the time of screening were excluded from the study.

Procedures

Through prenatal examination at 11^{+0}–13^{+6} week of gestation, maternal characteristics and medical histories were recorded [14]. MAP was measured according to standardized protocol by validated automated devices (BP3AQ1 Microlife, Taipei, Taiwan) [15]. UtAPI was obtained from left and right uterine arteries through pulsed-waved Doppler ultrasound imaging [16]. All operators had received Certificate of Competence from FMF. PlGF in serum was measured by automated analyzer, B·R·A·H·M·S KRYPTOR analyzer (ThermoFisher Scientific, Hennigsdorf, Germany). All investigators were provided with training for all procedures in advance. Consistent collection of data was maintained throughout study period.

Outcome measures

Pregnancy outcome was collected from general practitioners of women or hospital maternity records. Based on the definition from ACOG, PE was diagnosed by preexisting or pregnancy-associated hypertension [7]. Preterm and term PE were defined with delivery with PE at ≤37th and >37th week of gestation, respectively [17].

Statistical analysis

To normalize the data from FMF triple test, measured values of MAP, UtAPI and PlGF were converted into MoM. East Asian-specific biomarkers MoM formula was determined by multivariate regression analysis of maternal characteristics contributing substantively to $\log_{10}$ transformed value [18]. MoM values of MAP, UtAPI and PlGF in unaffected, all, preterm and term PE group were analyzed by one-way ANOVA.

Based on Bayes theorem-based model from FMF, patient-specific risks of PE were calculated by a combination of maternal characteristics and MoM values of three biomarkers with the software of ASTRAIA (version 1.26.1) [19–21]. Performance of screening for PE by FMF triple test was assessed by examining the ability to discriminate between PE and non-PE group [22]. Area under the receiver operating characteristic (AUROC) and detection rate (DR) at fixed false-positive rate (FPR) of 5%, 10%, 15% and 20% were utilized to evaluate discrimination. Regarding statistical software, Prism version 8.0.1 (GraphPad Software Inc., San Diego, CA, USA) was used for data analysis and receiver operating characteristic (ROC) curve analysis.

Results

Distribution of biomarkers

Of 700 pregnancies in the study, 3.57% (25 of 700) of the cases experienced PE. The incidences of all, preterm and term PE were 3.57%, 1.14% and 1.85%, respectively. Comparison of MoM of three biomarkers was shown in Fig. 1. The mean MAP MoM of women with preterm 1.096 (95% confidence interval [CI], 1.025–1.166), all PE 1.073 (95% CI, 1.030–1.117) and term PE 1.063 (95% CI, 1.003–1.122) were higher than that without PE 1.000 (95% CI, 0.994–1.007) with no significant difference. The mean UtAPI MoM of women with preterm 1.084 (95% CI, 0.809–1.360), all PE 1.078 (95% CI, 1.960–1.195) and term PE 1.075 (95% CI, 0.935–1.215) were higher than that without PE 1.035 (95% CI, 1.008–1.063) with no significant difference. The mean PlGF MoM of women with preterm 0.927 (95% CI, 0.632–1.223), all PE 0.975 (95% CI, 0.851–1.099) and term PE 0.997 (95% CI, 0.852–1.142) were lower than that without PE 1.031 (95% CI, 0.992–1.070) with no significant difference.

Performance of screening

To evaluate the performance of screening for PE, AUROC and DR of model are effective indicators. Comparison of DR at different FPR was showed in Table 1. ROC curve of screening for all, preterm and term PE were shown in Fig. 2. For screening of all PE, FMF triple test had an AUROC of 0.7330 (95% CI, 0.6479–0.8182) and DR of 8.0%, 20.0%, 32.0% and 48.0% at FPR of 5%, 10%, 15% and 20%. These results corresponded to risk cut-offs of 1 in 50, 1 in 98, 1 in 153 and 1 in 213, respectively. For screening of preterm PE, FMF triple test had an AUROC of 0.7876 (95% CI, 0.6482–0.9270) and DR of 12.5%, 50.0%, 50.0% and 62.5% at FPR of 5%, 10%, 15% and 20%. These results corresponded to risk cut-offs of 1 in 50, 1 in 98, 1 in 152 and 1 in 208, respectively. For screening of term PE, FMF triple test had an AUROC of 0.7016 (95% CI, 0.5990–0.8041) and DR of 5.9%, 11.8%, 17.7% and 41.2% at FPR of 5%, 10%, 15% and 20%. These results corresponded to risk cut-offs of 1 in 50, 1 in 97, 1 in 146 and 1 in 208, respectively.

Discussion

Biomarkers for screening of preterm PE

Our PlGF levels were specifically lower in both preterm and term PE groups. Consistent with previous study, the East Asian have lower PlGF level than the Caucasian because of their smaller placental size, that might lead to high FPR and poor performance of screening [23].

Standardization of acquiring biomarker was essential to improve performance of screening. In previous study in Chinese population, lower DR was noted due to improper measurement of blood pressure and pulsatility index without FMF protocol [24]. Therefore, training for all procedure according FMF criteria was provided in advance to obtain precise data in our study.

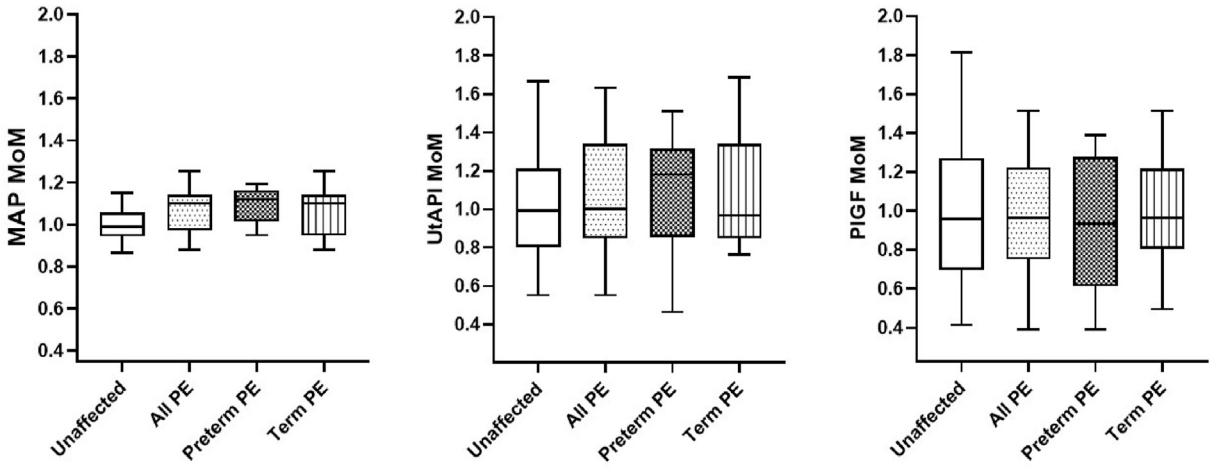

Fig. 1. Box plots of MoM of MAP, UtAPI and PlGF in unaffected, all, preterm and term PE group. MAP: Mean arterial pressure; MoM: Multiples of the median; PlGF: Placental growth factor; PE: Preeclampsia; UtAPI: Uterine artery pulsatility index.

Table 1
Performance of screening of all, preterm and term PE.

FPR, %	Risk cut-off (1 in x)[a]	DR, %	Confidence interval, %
All PE			
5%	50	8.00	1.42–24.97
10%	98	20.00	8.86–39.13
15%	153	32.00	17.21–51.59
20%	213	48.00	30.03–66.50
Preterm PE			
5%	50	12.50	0.64–47.09
10%	98	50.00	21.52–78.48
15%	152	50.00	21.52–78.48
20%	208	62.50	30.57–86.32
Term PE			
5%	50	5.88	0.30–26.98
10%	97	11.76	2.09–34.34
15%	146	17.65	6.19–41.03
20%	208	41.18	21.61–63.99

DR: Detection rate; FPR: False-positive rate; PE: Preeclampsia.
[a] "x" indicates number in the column. A screen positive test indicates women with risk more than "1 in x".

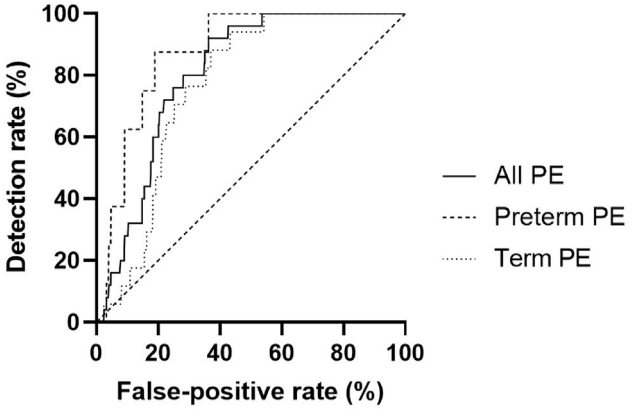

Fig. 2. ROC curves for screening of all, preterm and term PE. PE: Preeclampsia.

Performance in screening of preterm PE

Consistent with previous studies in Asian population, FMF triple test achieved high DR of 12.5%, 50.0%, 50.0% and 62.5% at FPR of 5%, 10%, 15% and 20% in Taiwan [12]. Nonetheless, screening performance of PE in Asia was inferior to that in Europe [9]. First, frequency of PE and risk factor were lower in the Asian. These geographic differences might be derived from living standard, accessibility to healthcare and sociodemographic factors [25].

Compared with ACOG and NICE model, FMF triple test had better performance in screening of PE, that was consistent in Asian and European populations [9,12]. ACOG and NICE treated each maternal characteristic as a separated test with FPR and additive detection. However, FMF calculated prior risk with multivariate regression analysis of maternal characteristics. Then, Patient-specific risks were generated with different relative importance from every maternal characteristic and adjustment according to biophysical and biochemical factors [14].

Implication of clinical practice

Taiwanese pregnant women are requested to attend for their routine first antenatal visit at 11^{+0}-13^{+6} week of gestation. Maternal characteristics and medical history were recorded based on the guideline from FMF. MAP could be measured by healthcare assistants with minimal training according to the protocol. The procedure merely took a few minutes with an inexpensive equipment. UtAPI should be measured by same qualified sonographers and ultrasound machines. Only additional 2–3 min beyond original test of Down screening (around 10 min) were needed to scan the flow of uterine artery. PlGF in serum could be measured with same blood sample and automated platform of associated plasma protein-A and β-human chorionic gonadotropin, important biochemical factors in screening of Down syndrome [26]. The calculation of patient-specific risk for PE was available with the software ASTRAIA. All components of PE screening were similar with those of Down screening which were well developed for a long time. With good performance of this study, first trimester screening for PE has been regularly implemented in our hospital. High compliance was noted because of no excessive intervention for pregnant women. As the second reason of maternal death in pregnancy, early prediction of PE was suggested by special bodies. Therefore, integration of PE and Down screening could generate a one-step workflow as daily practice in Taiwan.

Strengths and limitations

This is the first study for evaluation of first trimester screening of PE in Taiwan. Maternal characteristics and medical histories were

prospectively collected from routine examination in a specific GA range. All biomarkers were acquired with standardized approaches and converted into MoM based on East Asian-specific formula. As a result, screening model was properly applied to estimate patient-specific risk of PE.

Our participants represented a relatively small sample size. Model overfitting might happen due to data collection from only single center. Besides, some participants were prescribed Aspirin (100 mg/day) due to predictable elevated risk of PE based on their maternal characteristics. With the treatment of Aspirin, some screen-positive participants might be transformed into false-positives, that might reduce the DR of model.

Conclusion

For proper prophylaxis of Aspirin, effective screening of PE is indispensable in first trimester. Consistent with previous study in Asia, FMF triple test showed high DR for preterm PE in Taiwan. First Taiwan prospective and non-interventional study to screen the preeclampsia in first trimester pregnancy showed the effective workflow for daily practice.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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