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Role of Fetal Medicine Foundation (FMF) Instrument as a Screening Pre-eclampsia: A Cohort Study

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Abstract

Background: Maternal death is still a problem among pregnant women. One of the most prevalent causes of maternal death is preeclampsia. Preeclampsia contributes not only to maternal death, but also increases fetal morbidity. Early screening for preeclampsia is a key factor to managing the condition. The Fetal Medicine Foundation (FMF) has developed an algorithm to predict preeclampsia during the first trimester of pregnancy. However, there has been lack of studies done in Indonesia its usage. Therefore, this study aims to examine the accuracy of the FMF algorithm as a screening tool to identify preeclampsia in women in the first trimester of pregnancy Methods: Prospective cohort study done in Obstetrics and Gynecology Department of Mohammad Hoesin Hospital Palembang in January-December 2023. Sixty subjects that met the inclusion criteria were followed from 11 to 13+6 weeks to birth. All subjects undergo history taking for maternal and obstetrics history, physical examination, in particular mean arterial pressure (MAP) measurement, ultrasonography examination to evaluate mean uterine artery pulsatility index (UtA-PI), crown-rump length (CRL), and laboratory testing for pregnancy-associated plasma protein-A [PAPP-A] and placental growth factor [PlGF]. The outcome of this study is the incidence of preeclampsia as well as the detection rate (accuracy rate), false positive rate, positive predictive value (PPV), and negative predictive value (NPV) of the FMF algorithm. Data were analyzed using SPSS version 25.0 with a significance level of p <0.05 and a 95% CI. Kolmogorov Smirnov test was used for data homogeneity, Chi-square or Fisher test for categorical data, One way anova and Kruskal wallis test for numerical data. Results: Sixty subjects were enrolled. Among these, 30 subjects subsequently developed preeclampsia, with 18 (30%) experiencing early-onset preeclampsia, 12 (20%) experiencing late-onset preeclampsia, and 30 (50%) not developing preeclampsia (normotension). There was no significant difference in maternal characteristics and obstetric history among the three groups. MAP is found to be significantly different, with the highest found in the early onset preeclampsia group (p=0.021). Uterine artery pulsatility index (UtA-PI) was significantly higher in early-onset and late-onset preeclampsia subjects (p=0.019). There was no significant difference among the three groups in CRL. Serum PIGF was significantly lower in early onset and late-onset preeclampsia subjects (p-0.0001). Serum PAPP-A is also significantly lower in the early-onset preeclampsia subjects (p=0.0002). The combination of FMF/MAP, UtA-PI, yields the highest accuracy in predicting preeclampsia with 100% values for sensitivity, specificity, PPV, and NPV (p=0,000). The other combinations

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show lower accuracy, but quite good values of specificity and sensitivity. Conclusion: The FMF algorithm is an accurate screening tool to identify preeclampsia in the first trimester of pregnancy.

Keywords: *Pre-Eclampsia, Screening, Fetal Medicine Foundation.*

Introduction

Maternal death is still a problem among pregnant women living in Southeast Asia. In Indonesia, recent data showed about 230 deaths 100.000 live births.[1] One of the most prevalent causes of maternal death is preeclampsia. Globally, around 12% of pregnant women worldwide die from preeclampsia. The World Health Organization (WHO) estimates that the incidence of preeclampsia was found to be seven times higher in developing countries compared to developed countries. The prevalence of preeclampsia ranges between 1.8% to 16.7% in developing countries.[2]

Preeclampsia contributes not only to maternal death but also increases fetal morbidity. Babies born from this condition are at risk of low birth weight, intrauterine growth restriction, developmental delays, and other problems. In addition, preeclampsia is also associated with long-term cardiovascular-related diseases for the mother.[3-6] Preeclampsia is characterized by placental dysfunction and increased maternal response to systemic inflammation with endothelial activation and coagulation. This condition occurs due to the interaction of various factors including maternal, fetal, and placental factors. Several factors that are currently considered important include placental implantation with abnormal trophoblastic invasion of the uterine blood vessels, maternal maladaptation to cardiovascular changes, maladaptive immunological tolerance, and genetic factors.[7]

The diagnosis of preeclampsia is made based on the presence of hypertension specifically caused by pregnancy accompanied by organ dysfunction at gestational age above 20 weeks. Previously, preeclampsia was always defined by the presence of hypertension and proteinuria that recently occurred in pregnancy. Although these two criteria are still included in classic definitions of preeclampsia, several other organ damages could also occur; even when the patient does not experience proteinuria.[8-11]

The Fetal Medicine Foundation (FMF) is a registered charity which aims to improve the health of pregnant women and babies through feto-maternal medicine research and training. FMF has developed an algorithm to predict preeclampsia during the first trimester of pregnancy. The algorithm has been proven to have high discriminatory capabilities where 75% of cases of preterm preeclampsia (occurring before 37 weeks of gestation) were correctly detected with a false positive rate of 10%. This algorithm measures several factors such as maternal characteristics, biophysical markers (including body mass index [BMI] and mean arterial pressure [MAP]), chemical markers (including pregnancy-associated plasma protein-A [PAPP-A] and placental growth factor [PlGF]), and mean uterine artery pulsatility index (UtA-PI) which all can be completely assessed during one antenatal visit at 11 to 14 gestation weeks.[9]

Boutin et al (2021) published a cohort study in North America that shows, at least 1 in 10 women who identified as having high risk based on the FMF algorithm experienced at least one pregnancy complication mediated by the placenta.[9] Various countries such as the United States, Brazil, Australia, China, Hong Kong, Taiwan, Japan, Thailand, and Singapore have validated the use of this FMF algorithm.[8] However, there have been no studies done in Indonesia about

the validation and usage of the FMF algorithm as an instrument in detecting preeclampsia in the first trimester of pregnancy. Therefore, this study aims to examine the accuracy of the FMF algorithm as a screening tool to identify preeclampsia in women in the first trimester of pregnancy.

Methods

A prospective cohort study was conducted to assess the accuracy of the FMF algorithm as a screening tool to identify preeclampsia in pregnant women in their first trimester. The study was done in the Obstetrics and Gynecology Department of Mohammad Hoesin Hospital Palembang in January-December 2023.

Subjects include pregnant women with gestational age that ranges from 11 to 13^{+6} weeks that met inclusion criteria. Inclusion criteria were a single live fetus with head presentation, gestation age between 11 to 13^{+6} weeks, and has agreed to join this study and signed an informed consent form. Exclusion criteria were multiple pregnancies, pregnancy with a fetal abnormality that is lethal, a chromosomal abnormality that ends with pregnancy termination before 14 weeks gestational age, fetal death before 14 weeks gestational age, and history of acetylsalicylic acid consumption before pregnancy. Dropout criteria for the cohorts include fetal death, loss to follow-up, and subjects refusing to continue being part of the study.

The minimum sample size for each group was 23 subjects. To reduce the risk of dropout from the study, the number of participants was increased by 20%, so that each group has 28 subjects. In total, there were 56 minimum subjects needed to be included in this study. A consecutive sampling method was used, where every subject that met the inclusion criteria was included in the study.

Subjects that met inclusion criteria and had signed informed consent underwent thorough history taking and physical examination. Age, address, education level, income, and parity were collected and obstetric physical examination was also performed. Other data that were taken include ethnicity, smoking status, contraception usage history, and chronic illness (hypertension, diabetes mellitus, and anti-phospholipid syndrome). On physical examination, we measured the weight and height of the subjects to count body mass index and also mean arterial blood pressure. Subjects then underwent ultrasonography examination performed by fetomaternal doctors. Data collected were crown-rump length and mean uterine artery pulsatility index (UtA-PI). Subjects then underwent laboratory testing for pregnancy-associated plasma protein-A [PAPP-A] and placental growth factor [PlGF]. Samples were taken by nurses or the research team in the obstetric clinic. Lab testing was done in an external laboratory, Prodia laboratory. Samples were stored at room temperature for 30 minutes and then centrifuged with 3000 G for 10 minutes at the temperature of 4 C. Supernatants were collected and stored at -80 C for examination. Detection of PAPP-A and PlGF levels were performed with ELISA.

Subjects then were followed up till birth. Examination was performed once in the second trimester (<34 weeks gestational age) and once in the third trimester (>34 weeks gestational age). Mean arterial pressure measurement was performed by the research team or resident who works in the obstetrics clinic.

The data collected was inserted in the FMF algorithm. The FMF Algorithm that was used is from the official FMF website. FMF is an online-based instrument developed by the Fetal Medicine Foundation (FMF) that combines maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and pregnancy-associated plasma protein-A (PAPP-

A)/placental growth factor (PlGF) to predict the occurrence of preeclampsia in the first trimester. The result can be classified as high risk and low risk. Low risk is defined when the cut-off of the FMF score is >1/100. Whereas high risk is defined when the cut-off of FMF score is<1/100.[9]

The main outcome of this study is the incidence of preeclampsia. Preeclampsia is defined as blood pressure readings of systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg after 20 weeks of gestation in previously normotensive women, or the presence of urinary protein ≥ 0.3 grams in a 24-hour urine collection (or a dipstick urine test result of ≥ 1+), with or without the occurrence of symptoms such as central nervous system (CNS) disturbances, visual disturbances, pulmonary edema, epigastric pain or right upper quadrant pain, impaired liver function, thrombocytopenia, and oliguria. We also differentiate the incidence of early-onset and late-onset preeclampsia. Early onset preeclampsia is defined when the condition is diagnosed at gestational age >20 weeks and <34 weeks. Late-onset preeclampsia is defined as when the condition is diagnosed at>34 weeks gestational age.

All collected data were recorded and coded, followed by univariate analysis. Data is shown in frequency distribution tables and narratives. The normality test is done with the Kolmogorov-Smirnov method. Data that are normally distributed is presented as mean ± standard deviation (SD). Whereas data that are not normally distributed is presented as median (minimum-maximum). Categorical data is presented as n (%) and analyzed using the Chi-square test or Fisher's exact test as appropriate. To assess the diagnostic capability of the FMF algorithm in predicting preeclampsia in pregnant women during the first trimester, we calculate the detection rate (accuracy rate), false positive rate, positive predictive value, and negative predictive value of the FMF algorithm. The data will be processed using SPSS software version 25.0 with a significance level of $p < 0.05$ and a 95% Confidence Interval (CI).

Results

A total of 60 subjects with gestational ages between 11 and 14 weeks. Among these, 30 subjects subsequently developed preeclampsia, with 18 (30%) experiencing early-onset preeclampsia, 12 (20%) experiencing late-onset preeclampsia, and 30 (50%) not developing preeclampsia.

1. Normality test

The results of the normality test using the Kolmogorov-Smirnov method indicate that age, weight, height, body mass index, mean arterial pressure and uterine arterial pulsatility index are normally distributed; therefore, the mean values will be presented as mean ± standard deviation (SD). In contrast, placental growth factor (PlGF) and Pregnancy-Associated Plasma Protein-A (PAPP-A) are not normally distributed, so their values will be presented as median (minimum-maximum).

Variable	Statistics	p-value	Data distribution
Age, mean (years)	0.0118	0.401	Normal
Weight (Kg)	0.083	0.200*	Normal
Height (Cm)	0.095	0.200*	Normal
Body mass index (Kg/Cm^2)	0.094	0.200	Normal
Mean Arterial Pressure	0.095	0.200*	Normal

Uterine Arterial Pulse	0.112	0.063	Normal
Serum placental GF	0.201	0.000	**Not normal**
Serum PAPP-A	0.460	0.000	**Not normal**

Table 1. Normality test with Kolmogorov-Smirnov test

*Kolmogorov Smirnov test, distribution is normal when p>0.05

2. Preeclampsia incidence

There are 30 normotensive subjects and 30 subjects who subsequently develop preeclampsia, where 18 subjects (30.0%) are classified as having early-onset preeclampsia and 12 subjects (20.0%) are classified as having late-onset preeclampsia.

Subjects distribution	**n**	**%**
Normotension	30	50.0
Early onset pre-eclampsia	18	30.0
Late-onset pre-eclampsia	12	20.0
Total	60	100.0

Table 2. Preeclampsia Incidence Distribution

3. Maternal Characteristics and Obstetrical History

The ages of subjects with early-onset and late-onset preeclampsia were 26.71±5.21 and 29.615±4.87 years respectively, which did not differ significantly from the ages of normotensive subjects, who were 28.33±4.49 years (p=0.254). The average height of subjects with early-onset and late-onset preeclampsia was 159±5.60 cm and 160±6.80 cm, respectively, compared to 160±4.30 cm for normotensive subjects (p=0.532). Similarly, weight did not differ significantly among the three groups: 56.7±7.80 kg for early-onset preeclampsia, 60±6.90 kg for late-onset preeclampsia, and 58.43±8.3 kg for normotensive subjects (p=0.817). Body mass index (BMI) also showed no significant difference among the three groups, with an average of 22 kg/m^2 (p=0.589). Smoking history during pregnancy was noted in only 1 (5.88%) subject with early-onset preeclampsia and was absent in both late-onset preeclampsia and normotensive groups (p=0.276). All cases had a history of natural conception.

There were 3 (17.65%) subjects with early-onset preeclampsia who had a history of chronic hypertension, whereas no subjects with late-onset preeclampsia or normotensive subjects had a history of chronic hypertension. This indicates a significant difference between preeclampsia in general and normotensive pregnancies (p=0.018). No subjects had a history of systemic lupus erythematosus (SLE), while a history of Antiphospholipid syndrome (APS) was found only in the group without preeclampsia, with 2 cases (6.67%). There was no significant difference in the distribution of APS among the three groups (p=0.355). Primiparity was found in 11 subjects (61.11%) of early-onset preeclampsia, 10 subjects (83.33%) of late-onset preeclampsia, and 13 subjects (43.33%) in the normotensive group. Multiparity was found in 7 subjects (38.88%) of early-onset preeclampsia, 2 subjects (16.66%) of late-onset preeclampsia, and 17 subjects (56.66%) in the normotensive group. There was no significant difference in the distribution of childbirth history between the groups (p=0.602). Based on medical and obstetric history, the Chi-square test results indicated no significant differences among the three groups.

Maternal characteristics	**Preeclampsia (n=30)**		**Normotension (n=30)**	**p**
	Early onset (n=18)	**Late-onset (n=12)**		
Age (years)	26,71±5,21	29,615±4,87	28,33±4,49	0,254[a]
Height (cm)	159±5,60	160±6,80	160±4,30	0,532[a]
Weight (kg)	56,7±7,80	60±6,90	58,43±8,3	0,817[a]
BMI (kg/m^2)	22,38±3,27	23,52±2,43	22,81±3,05	0,589[a]
Medical history, n (%)				
Smoking history				
Yes	1 (5,88)	0 (0)	0(0)	0.276[b]
No	16(94,12)	12 (100)	30 (100)	
Natural conception				
Yes	18(30)	12(20)	30(50)	1,000[a]
No	0(0)	0(0)	0(0)	
Hypertension				
Yes	3 (17,65)	0(0)	0(0)	0,018[c]
No	14(82,35)	12(100)	30(100)	
Diabetes mellitus				
Yes	1(5,88)	1(7,69)	0(0)	0,342[c]
No	16(94,12)	12(82,31)	30 (100)	
Antiphos-pholipid syndrome				
Yes	0(0)	0(0)	2(6,67)	0,355[b]
No	18(100)	12(100)	28(93,33)	
Systemic lupus erythema-tosus				
Yes	0(0)	0(0)	0(0)	1,000[b]
No	18(100)	12(100)	30(100)	
Obstetric history				
Primiparous	11(61,11)	10(83,33)	13(43,33)	0,602[b]
Multiparous	7(38,88)	2(16,66)	17(56,66)	

Table 3. Comparison Of Maternal Characteristics and Obstetric Medical History in Cases of Early-Onset Preeclampsia, Late-Onset Preeclampsia, And Normotensive Pregnancies

*a) T-test; b) Fisher exact test, p is significant when p<0,05 c) Chi-square, p is significant when p<0,0

4. Biophysical characteristics

Based on the One-way ANOVA test, there is a significant difference in Mean Arterial Pressure (MAP) among the three groups (p=0.021). Early-onset preeclampsia subjects had the highest mean MAP (94.12±9.99 mmHg), while the late-onset preeclampsia and normotensive groups had similar means of 85.24±9.04 mmHg and 88.5±7.84 mmHg, respectively. Late-onset preeclampsia differed significantly from early-onset preeclampsia, with a p-value of 0.021. The biophysical characteristics among the three groups showed that the Uterine Artery Pulsatility Index (UtA-PI) was significantly higher (p=0.019) in early-onset preeclampsia subjects

(2.31±0.73) and the late-onset preeclampsia subjects (1.88±0.91) compared to the normotensive subjects (1.69±0.59). Early-onset preeclampsia was significantly different from normotensive, with a p-value of 0.019. In this study, there was no significant difference in fetal crown rump length (CRL) (p=0.024).

Characteristics	**Preeclampsia**		**Normotension**	**p**
	Early onset	**Late-onset**		
Mean arterial pressure (MAP)	94,12±9,99[a]	85,24±9,04[a]	88,5±7,84	0,021
Uterine arterial pulse index (UtA-PI)	2,31±0,73[b]	1,88±0,91	1,69±0,59	0,019
Fetal CRL	6,6±1,40	6,2±1,22	5,8±1,32	0,224

Table 4. Comparison of Biophysical Characteristics in Cases of Early-Onset Preeclampsia, Late-Onset Preeclampsia, and Normotensive Pregnancies

*One-way ANOVA test, with a p-value considered significant if $p < 0.05$; a) Late-onset differs significantly from early-onset, with a p-value of 0.021; b) Early-onset differs significantly from normotensive, with a p-value of 0.019.

5. Biochemistry Markers

Serum placental growth factor (PlGF) was tested using the Kruskal-Wallis test and was found to be significantly lower (p=0.0001) in early-onset and late-onset preeclampsia subjects, with medians of 37.68 (7.91-173.3) pg/mL and 37.61 (16.14-64.27) pg/mL, respectively, compared to the normotensive subjects, which had a median of 100.6 (44.39-360) pg/mL. Similarly, serum Pregnancy-Associated Plasma Protein-A (PAPP-A) levels were significantly lower (p=0.0002) in early-onset preeclampsia subjects, with a median of 3,567 (4-15,160) mU/L, compared to normotensive subjects, which had a median of 11,380 (2,340-39,810) mU/L.

Characteristics	**Preeclampsia**		**Normotension**	**p**
	Early onset	**Late-onset**		
Serum placental growth factor (PIGF) (pg/mL	47,68(7,91-173,3)[b]	37,61(16,14-64,27)[c]	100,6(44,39-360)	0,0001
Serum pregnancy-associated plasma protein-A (PAPP-A) (mU/L)	3,567(4-15.160)[b]	1,88±0,4,232(1,291-15,860)[c]	11,380(2,340-39,810)	0,002

Table 5. Comparison of Biochemistry markers in Cases of Early-Onset Preeclampsia, Late-Onset Preeclampsia, and Normotensive Pregnancies

*Kruskal-Wallis test, with a p-value considered significant if $p < 0.05$; b) Early-onset differs significantly from normotensive; c) Late-onset differs significantly from normotensive.

6. Efficacy of FMF Algorithm for Preeclampsia Screening

In this study, the diagnostic capability of the FMF algorithm in predicting preeclampsia was evaluated in several combinations, including the accuracy of FMF/MAP and UtA-PI, the accuracy of FMF/MAP, UtA-PI, and PAPP-A, FMF/MAP, UtA-PI, and PlGF, as well as FMF/MAP, UtA-PI, PlGF, and PAPP-A as additional analyses in predicting the occurrence of preeclampsia. In addition, analyses for each group; early-onset and late-onset preeclampsia, were also done.

The combination of FMF/MAP and UtA-PI has a 100% value for sensitivity, specificity, positive predictive value, and negative predictive value (p=0.000). This suggests that the FMF/MAP and UtA-PI measurements are accurate in predicting preeclampsia. The combination of FMF/MAP, UtA-PI and PlGF shows 100% value for sensitivity, specificity, and positive predictive value. However, it still has a negative predictive value of 3,3% (p=0,000). Overall, this combination has a high accuracy of 96,7% to predict preeclampsia.

The combination of FMF/MAP, UtA-PI and PAPP-A shows lower values of sensitivity (60%), specificity (80%), PPV (96,77), and NPV (100), which is significant (p=0.000). The highest value is 80% for specificity. Therefore, this combination is specific to predict preeclampsia. The combination of FMF/MAP, UtA-PI, and PLGF shows also moderate values of accuracy, with 90% sensitivity, 73,3% specificity, 77,14% positive predictive value, and 88% negative predictive value (p=0,000).

Combination of measurements	**Preeclampsia**				
	Sn	**Sp**	**PPV**	**NPV**	**Accuracy**
FMF/MAP, UtPI	100	100	100	100	100
FMF/MAP, UtPI & PlGF	100	96,7	96,77	100	96,7
FMF/MAP, UtPI & PAPP-A	60	80	75	33,3	50
FMF/MAP, UtPI, P1GF & PAPP-A	90	73,3	77,14	88	63,3

Table 6. Preeclampsia Screening with FMF Algorithm

The combination of FMF/MAP and UtA-PI also has 100% value for sensitivity, specificity, positive predictive value, and negative predictive value in predicting early onset preeclampsia (p=0.000).

The combination of FMF/MAP, UtA-PI and PlGF shows quite good accuracy in predicting early-onset preeclampsia with quite high value for sensitivity (100%), specificity (96,67%), positive predictive value (97,74%), and negative predictive value (100%). This result is also significant statistically using the Fisher exact method (p=0,000).

The combination of FMF/MAP, UtA-PI dan PAPP-A shows a lower value for sensitivity (100%), specificity (80%), PPV (75%), and NPV (100%) for predicting early onset preeclampsia (p=0.000). Therefore, this combination's accuracy is about 80%

The combination of FMF/MAP, UtA-PI and PIGF shows sensitivity in predicting late-onset preeclampsia (100%). However, it has lower values of specificity (76,67%) and positive predictive value (75%), making its accuracy the lowest, at about 76,67% (p=0,000).

Combination of measurements	Early onset preeclampsia				
	Sn	**Sp**	**PPV**	**NPV**	**Accuracy**
FMF/MAP, UtPI	100	100	100	100	100
FMF/MAP, UtPI & P1GF	100	96,67	97,74	100	96,67
FMF/MAP, UtPI & PAPP-A	100	80	75	100	80
FMF/MAP, UtPI, P1GF & PAPP-A	100	76,67	72	100	76,67

Table 7. Early-onset Preeclampsia Screening Combination with FMF Algorithm

The combination FMF/MAP and UtA-PI also has 100% value for sensitivity, specificity, positive predictive value, and negative predictive value in predicting late-onset preeclampsia (p=0.000). The combination of FMF/MAP, UtA-PI dan PlGF shows quite good accuracy in predicting late-onset preeclampsia with quite high value for sensitivity (100%), specificity (96,67%), positive predictive value (92,31%), and negative predictive value (100%). This result is also significant statistically using the Fisher exact method (p=0,000).

The combination of FMF/MAP, UtA-PI dan PAPP-A shows a lower value of sensitivity (0%), specificity (80%), PPV (0%), and NPV (66,6%) for predicting late-onset preeclampsia (p=0.000). Therefore, this combination could be specific in predicting the incidence of late-onset preeclampsia. Whereas, the combination of FMF/MAP, UtA-PI and PLGF shows lower values of accuracy in predicting late-onset preeclampsia, with 83,3% sensitivity, 76,67% specificity, 58,82% positive predictive value, and 92% negative predictive value (p=0,000).

Combination of measurements	Late-onset preeclampsia				
	Sn	Sp	PPV	NPV	Accuracy
FMF/MAP, UtPI	100	100	100	100	100
FMF/MAP, UtPI & P1GF	100	96,67	92,31	100	96,67
FMF/MAP, UtPI & PAPP-A	0	80	0	66,6	80
FMF/MAP, UtPI, P1GF & PAPP-A	83,3	76,67	58,82	92	60,47

Table 8. Late-onset Preeclampsia Screening Combination with FMF Algorithm

Discussion

In this study, there was no significant difference in maternal characteristics among early-onset preeclampsia, late-onset preeclampsia, and normotension subjects, as the mean values in each group were not significantly different. Previous cohort studies done by Phil et al also showed that age was not significantly different in the early onset, late onset, and normotension groups.[12] In the case of body mass index, the study by Zwertbrok et al also showed no significant difference within the preeclampsia and normotensive group of subjects.[13] However, another

study published by Torres et al showed that the average age of subjects with early-onset and late-onset preeclampsia is higher, which was 35,11 years and 32,47 years respectively, compared to the normotensive group where the average age was 28,7 years.[14] Preeclampsia is associated with maternal characteristics such as age >40 years and BMI >30 kg/m². The risk of preeclampsia increases during adolescence and at maternal age ≥35 years. Advanced maternal age (≥35 years) is linked to an increased risk of cardiometabolic dysfunction and chronic diseases, multiparity, and the use of assisted reproductive technologies.[15]

Regarding medical and obstetric history, in this study, there was no significant difference between the three groups. However, for hypertension, three subjects with chronic hypertension subsequently developed early-onset preeclampsia. Two subjects had a history of diabetes mellitus and subsequently developed preeclampsia. A previous study by Torres et al (2023), showed that there were three subjects with DM and chronic hypertension and one subject with SLE who also had preeclampsia.[14] A long case-cohort study published by Tarca et al (2022) found that about 52,4% of subjects with early-onset preeclampsia and 29.7% of subjects with late-onset preeclampsia were nulliparous, but the result was not significant.[16] Another study done in Bangladesh also did not find the association that primiparity is a significant risk factor for preeclampsia.[2]

In our study, we found similar results where the history of births is not significant among the three groups. There were no subjects who had SLE at the time of study conception, whereas antiphospholipid syndrome was found only in the normotensive group. In a previous study by Mendoza et al, among the subjects who have late-onset preeclampsia, 5 (6,4%) had SLE and 1(1,3%) had APS, but these results were not significant.[17] Although some previous studies have shown no significant differences, maternal medical conditions can still be risk factors for preeclampsia as they are related to the formation of placenta and endothelial dysfunction. The non-significant findings in this study may be attributed to the relatively young average age of the subjects in each group, which is less than 30 years, resulting in a lack of significant comorbidities.

The biophysical characteristics in this study showed significant results for UtA-PI and MAP values among the three groups. Meanwhile, there were no significant value differences for fetal CRL among the three groups. A study by Torres et al showed also significant difference in MAP values between the three groups, where the highest value was found in late-onset preeclampsia (86,7 mmHg on average). Meanwhile, the value of UtA-PI is also significant, particularly in the early onset group, with a median value of 2,310±7.3 pg/mL.[14] A study from Barcelona conducted by Mendoza et al in 2022, which predicted the incidence of preeclampsia through first-trimester screening, found that the mean MAP for the late-onset preeclampsia group was 91.2 (82.8-96) mmHg and UtA-PI was 1.72 (1.31-2.15) pg/m. In contrast, for the early onset preeclampsia group, the mean MAP was higher at 95.1 (89.7-103) mmHg, and UtA-PI was 2.25 (1.89-2.92) pg/mL.[17] Through these previous studies, we can conclude that UtA-PI measurements have shown significant differences, with the highest levels found in early-onset preeclampsia. This is related to the increased PI, reflecting maladaptation to the changes during pregnancy. Impaired placentation is associated as a primary factor influencing both early-onset and late-onset preeclampsia.[18] MAP was found to have the highest value in early-onset preeclampsia. MAP reflects the ability of vascular adaptation during pregnancy.[19]

Regarding biochemistry characteristics, this study found significant differences in PlGF and PAPP-A levels between the groups, with the highest observed in the early onset preeclampsia

group. Torres et al also found a significant difference for PIGF, where the lowest serum P1GF was found in the early onset preeclampsia group (14,88 pg/mL on average).[14] A case-control study conducted by Kenny et al. in 2020 found that the preeclampsia group had a cut-off point for PlGF of 6 pg/mL, with a mean of 7.1 (5.7-8.9) pg/mL. Kenny et al. stated that among the numerous studies on biochemical markers for preeclampsia, PlGF is one of the most reliable indicators. Low serum PlGF levels during pregnancy are associated with disease phenotypes that exhibit placental insufficiency. Low PlGF levels early in pregnancy can serve as a predictor for preeclampsia, particularly early-onset preeclampsia.[20] Mendoza et al found that the mean PlGF levels in late-onset preeclampsia subjects were 28.8 (21-39) pg/mL, and in early-onset preeclampsia subjects the levels were 23.3 (19.3-27.9) pg/mL. The mean PAPP-A levels in late-onset preeclampsia cases were 1255.5 (721.6-1844) mU/L, and in early-onset preeclampsia cases, the levels were 1373 (748.7-2112) mU/L.[17] PlGF plays a role as a potent angiogenic factor that affects early placental vascularization and its levels decrease in preeclampsia.[21] PIGF levels increase during pregnancy, rising steadily until the 30th week of gestation. Patients with high PlGF levels have a low likelihood of experiencing preeclampsia. Levels above 100 pg/mL are considered normal PlGF levels.[22] In this study, high PlGF levels may be attributed to errors in data collection or laboratory testing. Low PAPP-A levels at 11-13 weeks of gestation are associated with stillbirth, fetal death, intrauterine growth restriction, preterm birth, and preeclampsia. Low PAPP-A levels are related to poor early placentation.[23]

In this study, the combination of FMF/MAP and UtA-PI showed the highest accuracy in predicting both early-onset and late-onset preeclampsia. The combination of FMF/MAP, UtA-PI, and PlGF also showed accurate predictive values, although not as high as the combination of FMF/MAP and UtA-PI alone. The combination of FMF/MAP, UtA-PI, PlGF, and PAPP-A demonstrated high sensitivity in predicting preeclampsia, Whereas the combination of FMF/MAP, UtA-PI, and PAPP-A showed specificity in predicting preeclampsia and late-onset preeclampsia but was accurate in predicting early-onset preeclampsia. A previous study by Malone et al showed that UtA-PI has 48% sensitivity and 92% specificity.[24] While Serrano et al studied the usage of a combination of FMF/MAP and UtA-PI, found a lower accuracy of 54,6% for early onset preeclampsia, and 43.4% for late-onset preeclampsia.[25] This difference could be caused by inter-operator differences while performing the Doppler ultrasound, different gestational age, and also race among the studies.

In another study, the combination of UtA-PI examination and PlGF biochemical markers in the FMF has an accuracy rate of 62% with a false positive rate of 10% in a population of pregnant women at 11-13 weeks of gestation. In this study, preeclampsia screening was conducted with a total of 50 metabolic markers. However, the model without UtA-PI showed a detection rate of 58%.[26] Serrano et al found that the best accuracy for predicting preeclampsia was found with the combination of FMF/MAP, UtA-PI, PlGF, and PAPP-A examinations. This combination of tests could detect 90.9% (with a range of 54.6%-100%) of early-onset preeclampsia and 63.4% (with a range of 43.3%-80%) of preeclampsia cases with gestational age <37 weeks. The study also found that adding PAPP-A did not improve the prediction accuracy of the algorithm when performed together with PlGF. However, in situations where PlGF is not available, PAPP-A can increase the detection rate by 5% when used in combination with certain markers.[25]

The FMF algorithm has proven to be more effective in detecting preeclampsia with delivery before 37 weeks of gestation or before 34 weeks of gestation when compared to conventional algorithms. A systematic review done in Ontario found that FMF screening at 11-13 weeks of gestation can reduce preeclampsia by a risk ratio of 64%- 70%.[27]

The limitations of this study include a relatively small sample size from only 1 site (hospital) and the timing of the blood sample processing. This simultaneous processing meant that the risk of preeclampsia could only be assessed after the laboratory results were available, resulting in the inability to administer aspirin to patients classified as high-risk promptly.

Conclusion

First-trimester preeclampsia screening with the FMF algorithm shows that the combination of FMF/MAP and UtA-PI yields the highest accuracy in predicting early-onset and late-onset preeclampsia. The combination of FMF/MAP, UtA-PI, and PlGF demonstrates a slightly lower accuracy in predicting preeclampsia. The combination of FMF/MAP, UtA-PI, and PAPP-A is specific in predicting preeclampsia and late-onset preeclampsia; but accurate in predicting early-onset preeclampsia. The combination of FMF/MAP, UtA-PI, PlGF, and PAPP-A is sensitive in predicting both early-onset and late-onset preeclampsia.

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No funding was received for this research. There was no conflict of interest in conducting this research.

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