Original Research Article

A comparative study of performance of first trimester FMF algorithm for prediction of preeclampsia in singleton and twin pregnancies in coastal Karnataka

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ABSTRACT

Background: Preeclampsia is one of the most common disorders of pregnancy known to complicate 5-10% of all the pregnancies, and it is a component of the deadly triad (along with haemorrhage and infection), that contributes greatly to maternal morbidity and mortality rates. The prevalence of preeclampsia in twin pregnancy is 3-4 fold compared to singleton pregnancy. Timely diagnosis and prevention of this condition is therefore critical. Multiple maternal factors and placental biomarkers have shown to predict preeclampsia in singleton pregnancies. Previous Studies have shown that the proposed algorithms for preeclampsia screening in singletons can also be applied in twins, but with slight modifications and lower accuracy.

Objective: To study the various parameters included in FMF screening algorithm in first trimester for preeclampsia in singleton and twin pregnancies. To find diagnostic accuracy of screening parameters to predict preeclampsia later in second and third trimester. To study sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) in singleton and twin pregnancy.

Materials and Methods: This prospective observational cohort study conducted in department of Obstetrics and Gynecology, Kasturba Medial College, Hospital, Manipal. Patients were recruited from August 2021 to November 2022. A total of 295 pregnant women were included of which 255 were singleton gestation and 40 were twin gestation. All parameters mentioned in FMF algorithm were obtained between 11week to 13+6 weeks. Patients were followed until delivery for occurrence of pre-eclampsia. Individual parameters of first trimester FMF algorithm of pre-eclampsia screening were analyzed in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) in both singleton and twin study subjects and results were then compared among the groups.

Results: In this study a total of 295 pregnant women were recruited. 255 were single gestation of which 47 had preeclampsia and 40 were twin gestation of which 4 had preeclampsia. In the cohort of singleton pregnant women with pre-eclampsia, mean age was noted to be higher (32.77±4.27). They had higher BMI (mean 27.61±3.74) and first trimester MAP was also higher. Similarly, cohort of twin pregnancy with preeclampsia had higher mean of maternal age, BMI and MAP (30.33 ±4.46, 22.83 ± 2.93 and 90.40 ± 1.45 respectively). The Preeclampsia group in both singleton and twin subjects had lower serum concentration and lower MoM values of PAPP-A and PlGF while higher values of free beta HCG and uterine artery PI. Therefore the FMF algorithm for first trimester screening of preeclampsia was found to be a good predictor in both singleton and twin pregnancy.

Conclusion: The first trimester FMF algorithm for preeclampsia screening had similar utility in the prediction of preeclampsia in both singleton and twin pregnancy with its individual parameters and combined risk model. However, its accuracy was slightly lesser among twins. Therefore, same screening model can be applicable in singleton and twin gestation.

1. Introduction

Preeclampsia (PE) is one of the most common disorders of pregnancy known to complicate 5-10% of all the pregnancies, and it is a component of the deadly triad (along with haemorrhage and infection), that contributes greatly to maternal morbidity and mortality rates.[1–3] As, etiology of PE is multifactorial, any information related to it could aid in detection and prevention of the disease. However, compared to women with singleton pregnancy, women with multiple gestation have greater rates of developing preeclampsia. It develops earlier, progresses more quickly, is more severe, and presents in an unusual way in twin pregnancies.

The FMF model, created by the Fetal Medicine Foundation, a British organisation is the most widely used technique for determining women who are at a high risk of developing PE. It was created based on the complex aetiology of PE and works well for detecting PE at the 11–13-week scan. With impressive predictive performance, the prediction model integrates clinical (maternal demographic traits), biochemical (S. PAPP-A & PlGF), and ultrasonographic information (first trimester uterine artery PI). In this process, also known as the FMF triple test, measures of the uterine artery pulsatility index (UTPI), pregnancy-associated plasma protein-A (PAPP-A), and placental growth factor (PLGF) are combined with information about the mother's health history.[4,5] Previous Studies have shown that the proposed algorithms for preeclampsia screening in singletons can also be applied in twins, but with slight modifications and lower accuracy. Therefore, in this study we aim to investigate and compare same in singleton and twin pregnancy.

2. Materials and Methods

A prospective observational cohort study conducted in department of Obstetrics and Gynecology, Kasturba Medial College, Hospital, Manipal over a period from August 2021 to November 2022. The study recruited a total of 295 pregnant women of which 255 were singleton gestation and 40 were twin gestation.

Buderer's method was used to compute the sample size at the desired degree of absolute precision for sensitivity and specificity. Obtained sample size was 255 singleton and 74 twin gestation. However, during the study period there were only 40 cases of twin pregnancy who registered for 11-14 weeks screening and delivered in this institution.

2.1. Inclusion criteria

1. Booked antenatal cases at KH Manipal.
2. Singleton and twin pregnancy.

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2.2. Exclusion criteria

1. Triplet and quadruplet gestation
2. Pre-existing cardiac, renal or pulmonary disease
3. Miscarriage or intra uterine death before 24 weeks
4. Fetal anomaly and cervical incompetence.

Twin and singleton pregnancies in first trimester were recruited from Kasturba hospital Manipal and informed consent was obtained. All parameters mentioned in FMF algorithm were obtained between 11week to 13+6 weeks. At 11–13+6 weeks, data of maternal demographic profile & characteristics were noted. The mean arterial pressure was measured. Uterine Artery mean PI at 11-13+6 weeks was measured. Maternal blood sample was tested for placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A). In addition, maternal serum beta HCG values were also obtained. Patients were followed until delivery for occurrence of pre-eclampsia. Gestational age at delivery was noted. Examination of placenta was done for chorionicity in twin pregnancy.

3. Results

3.1. Singleton pregnancy

In this study a total of 255 pregnant women with singleton pregnancy attending the antenatal clinic recruited in the study period and were followed until delivery, of which 47 had preeclampsia and 208 remained normotensive.

1. Table 1 shows cohort of singleton pregnant women with pre-eclampsia, mean age was noted to be 32.77±4.27, while that of normotensive singleton pregnant women was noted to be 30.2±4.17. The pre-eclamptic women were noted to be in higher age group.
2. Similarly, preeclamptic singleton pregnant women had higher BMI (mean 27.61±3.74) than normotensive singleton pregnancies (mean 21.5±3.17).
3. First trimester MAP was noted to be higher in pre-eclamptic pregnant women.
4. All three above mentioned parameters had statistically significant P value.

Table 2 shows that the Preeclampsia group had lower multiple of median of PAPP-A and PlGF while higher values of beta HCG MoM and uterine artery PI MoM.

MoM of PAPP-A, PlGF, beta HCG and UA PI, all had statistically significant P value.

3.2. Diagnostic parameters with FMF algorithm (Table 3)

1. The classical first trimester FMF preeclampsia prediction algorithm available in their website is meant for western population. Hence, had limited utility in our study.

Table 1: Maternal and pregnancy characteristics in singleton cohort: Mean and standard deviation (SD)

Baseline characteristics	Normotensive (208)	Preeclampsia (47)	F value	P value
Maternal age (years)	30.2 ± 4.17	32.77 ± 4.27	14	<0.001
Body mass index (bmi)	21.5 ± 3.17	27.61 ± 3.74	134	<0.001
Mean arterial pressure (map)	85.3 ± 3.28	93.20 ± 4.63	185	<0.001

Table 2: First trimester multiple of median of biochemical markers and uterine artery PI values in singleton cohort: mean and SD

Multiple of median	Normotensive (208)	Preeclampsia (47)	F value	P value
PAPP-A MOM	1.02 ± 0.05	0.78 ± 0.14	351	<0.001
PLGF MOM	1.02 ± 0.18	0.63 ± 0.21	158	<0.001
BHCG MOM	1.00 ± 0.25	1.46 ± 0.30	110	<0.001
Uterine artery PI MOM	1.01 ± 0.62	1.35 ± 0.43	12	<0.001

2. We conducted a logistic regression analysis with available parameters and derived various cutoff ratios and above table shows results for same.

3. In the model combining maternal factors, MAP, UA PI, PAPP-A and PlGF, with screen positive rate of 31%, risk cutoff of 1:75 showed sensitivity of 78.7%, specificity of 79.3%, PPV of 46.3% and NPV of 94.3%.

3.3. Twin pregnancy

After application of inclusion and exclusion criteria a total of 40 pregnant women with twin pregnancy attending the antenatal clinic recruited in the study period and were followed until delivery, of which 4 had pre-eclampsia and 36 were normotensive.

Table 4 shows arithmetic mean of maternal age, BMI and MAP was 30.33 ±4.46, 22.83 ± 2.93 and 90.40 ± 1.45 respectively.

Preeclampsia group had higher maternal age, body mass index and mean arterial pressure making them valuable clinical indicators.

Though the mean age of PE was more than normotensives, it didn't reach statistical significance due to small N (4) for PE. Mean arterial pressure and BMI had significant P value.

Table 5 shows that preeclampsia group had lower multiple of median of PAPP-A and PlGF while higher values of beta HCG MoM and uterine artery PI MoM.

MoM of PAPP-A, PlGF, beta HCG and UA PI, all had statistically significant P value.

With screen positive rate of 35%, at 1:75 risk cutoff, algorithm has FPR of 30.6%, sensitivity of 75%, specificity of 69%, PPV of 21%, NPV of 96% and diagnostic accuracy of 70%.

4. Discussion

Preeclampsia affects about 2%-3% of all pregnancies and accounts for 12% of maternal deaths and up to 25% of perinatal death worldwide. Timely diagnosis and prevention of this condition are therefore critical. Multiple maternal factors and placental biomarkers have shown to predict preeclampsia in singleton pregnancies. In twin pregnancies, preeclampsia is more common than in singletons. Previous Studies have shown that the proposed algorithms for preeclampsia screening in singletons can also be applied in twins, but with slight modifications and lower accuracy.[1,3]

Preeclampsia can be predicted with 96% sensitivity for a 10% false-positive rate using an integrated model recently proposed by the Fetal Medicine Foundation, which combines maternal preexisting risk factors, mean arterial pressure, uterine artery pulsatility index (PI), serum pregnancy-associated plasma protein A (PAPP-A), and placental growth factor (PlGF).[6,7]

In this study, using a combination of maternal features, mean arterial pressure (MAP), uterine artery doppler, and biomarkers in the first trimester of pregnancy, we seek to assess the effectiveness of the FMF first trimester preeclampsia screening model in singleton and twin pregnancies.

Our study proved that first trimester screening for preeclampsia using the FMF algorithm works effectively in our heterogeneous sample. The key strength of our work was the validation of the screening algorithm by investigation of the performance of each screening parameter. In contrast to published data, the incidence of PE in our population was remarkably low. This was another significant flaw in our study. Furthermore, we showed that the screening parameters employed for biochemical and biophysical analysis fell within the normal range for straightforward pregnancies. We reached nearly equal cut-offs in the various risk computations at a false-positive rate of 10%, and our rates of screen-positive results were likewise extremely similar to those described by the FMF London.

We studied 255 singleton pregnancies out of which 47 had preeclampsia. Women with preeclampsia had higher mean age (32.77±4.27), higher BMI (mean 27.61±3.74) and higher mean arterial pressure (mean-93.2 ± 4.6). Higher uterine artery PI and lower PAPP-A MoM and PlGF

Table 3: Predictive value of themodel at different risk cut off

Screen Positive Rate	Cut Off	False Positive Rate	Sensitivity	Specificity	PPV	NPV	Accuracy
4%	1:10	0.0%	21.3%	100.0%	100.0%	84.9%	85.5%
9%	1:25	1.9%	40.4%	98.1%	82.6%	87.9%	87.5%
15%	1:35	5.8%	55.3%	94.2%	68.4%	90.3%	87.1%
22%	1:50	12.0%	68.1%	88.0%	56.1%	92.4%	84.3%
31%	1:75	20.7%	78.7%	79.3%	46.3%	94.3%	79.2%
42%	1:100	31.7%	87.2%	68.3%	38.3%	95.9%	71.8%
54%	1:125	45.2%	93.6%	54.8%	31.9%	97.4%	62.0%
68%	1:150	61.1%	97.9%	38.9%	26.6%	98.8%	49.8%
83%	1:200	79.3%	100.0%	20.7%	22.2%	100.0%	35.3%
100%	1:250	100.0%	100.0%	0.0%	18.4%	100.0%	18.4%

Table 4: Maternal characteristics in twin cohort: Mean and standard deviation (SD)

Baseline characteristics	Normotensive (36)	Preeclampsia (4)	F value	P value
Maternal age (years)	30.33 ± 4.46	35 ± 2.94	4.15	0.50
Body mass index (BMI)	22.83 ± 2.93	29.31 ± 3.71	16.8	<0.001
Mean arterial pressure (MAP)	90.40 ± 1.45	99.45 ± 0.42	149	<0.001

Table 5: First trimester biochemical markers and uterine artery PIMoM values in twin cohort: mean and SD

Multiple of median	Normotensive (208)	Preeclampsia (47)	F value	P value
PAPP-A MoM	1.01 ± 0.05	0.68 ± 0.08	109	<0.001
PlGF MoM	0.98 ± 0.17	0.47 ± 0.25	28.94	<0.001
bHCG MoM	1.06 ± 0.71	2.05 ± 0.06	7.45	0.01
Uterine artery PI MoM	1.21 ± 0.23	1.53 ± 0.33	6.16	0.01

Table 6: Diagnostic parameters with FMF algorithm using 1:75 as cut off

Screen Positive Rate	Cut Off	False Positive Rate	Sensitivity	Specificity	PPV	NPV	Accuracy
35%	1:75	30.6%	75.0%	69.4%	21.4%	96.2%	70.0%

MoM were the most significant parameters in prediction of preeclampsia.

Prasad S et al. (2021)[8] conducted a prospective cohort study to assess the effectiveness of the Fetal Medicine Foundation's (FMF) preeclampsia (PE) screening method among 1863 women carrying singletons in New Delhi. Mean Arterial Pressure (MAP), transvaginal Mean Uterine Artery Pulsatility Index (UtAPI), and biochemical markers Pregnancy Associated Plasma Protein-A (PAPP-A) and Placental Growth Factor were used to screen the research participants for PE between 11 and 14 weeks of gestation. They had similar findings of higher mean age (31.4±3.6), higher BMI (mean 26.31±4.63) and higher mean arterial pressure (mean 92.4±4.1) in preeclampsia group. Both the study results showed lower MoMs of PAPP-A and PlGF in preeclampsia group. In our study with screen positive rate of 31%, risk cutoff of 1:75 showed sensitivity of 78.7%, specificity of 79.3%, PPV of 46.3% and NPV of 94.3%. But at risk cutoff of 1:50 the detection rate was 84% at false positive rate of 12%. Similar to our finding, Prasad S et al study at risk cut off of 1:45 had detection rate of 80% with false positive rate of 10%.[8] Finally, they concluded that while the FMF algorithm functioned as expected, it might be enhanced even more by properly adjusting biophysical and biochemical indicators for native South Asian women.

The lower Biochemical MoMs in our cohort is also consistent with those recently reported in a pan Asian study by Chaemsaithong and colleagues.[9]

Further, studies would be needed to assess interregional variation in maternal biochemistry levels across different Indian populations using standardized blood collection and processing protocol to determine whether levels reported in the earlier study are increased due to delayed processing of the blood sample or due to potential differences between analysis of fresh and previously frozen serum samples.

Parthasarathy K et al. (2022)[10] also conducted a prospective observational study in Chennai, India where 206 pregnant women participated to determine how well the extended first trimester screening test predicts pre-eclampsia. Out of 206, 12 women developed preeclampsia. Mean arterial pressure (MAP) had 66.7% sensitivity and 66.5% specificity in identifying pre-eclampsia but, P value (0.086) was not statistically significant. Where as our study showed MAP sensitivity and specificity 78.7% and 79.3% respectively with statistically significant P Value. Pregnancy-associated plasma protein-A (PAPP-A)

had high statistical significance with pre-eclampsia has a standalone marker. PAPP-A had 91.7% sensitivity and 87.1% specificity. This was a consistent finding in our study too. Similar to our study, their extended screening test (combination of all parameters) did a good job of identifying preeclampsia before it manifested clinically. [11,12]

Zwertbroek E et al. (2021) [13] carried out a prospective cohort study to assess the effectiveness of the first-trimester Fetal Medicine Foundation (FMF) screening algorithm for the prediction of preeclampsia in Netherlands. 362 singleton expectant women were enrolled in the research (nulliparous women and women with preeclampsia or intrauterine growth restriction in previous pregnancy). The patients were screened between weeks 11 and 14 of pregnancy to determine their preeclampsia risk. Six percent of the trial participants (n=22) had preeclampsia. In conclusion, the FMF algorithm performed satisfactorily for preeclampsia. Based on the ROC curves, optimal high-risk cutoff values for prediction of preeclampsia at any gestational age in this Dutch study population was 1:22, for this cutoff, the algorithm showed a sensitivity and specificity of 68% at a cost of false positive rate of 32% for the prediction of preeclampsia. PAPP-A were not significantly different between women who did and did not develop preeclampsia. Moreover, PAPP-A MoM, separately or in combination with the mean arterial blood pressure, was suggested as a predictor of preeclampsia this performance was inferior to our study results.

5. Conclusion

This comparative study of performance of first trimester FMF algorithm for prediction of preeclampsia in singleton and twin pregnancies in Coastal Karnataka concluded that twin pregnancies can also be screened for PE during the first trimester in the same way as singleton pregnancies are but with little modification.

Singleton pregnancies with preeclampsia had higher mean age, BMI and mean arterial pressure with good statistical significance. Higher uterine artery PI MoM, lower PAPP-A and PlGF MoM and serum concentration were the most significant parameters in prediction of preeclampsia. In the model combining maternal factors, MAP, UA PI, PAPP-A and PlGF, with screen positive rate of 31%, risk cutoff of 1:75 showed sensitivity of 78.7%, specificity of 79.3%, PPV of 46.3% and NPV of 94.3%.

In twin pregnancies mean age had no statistical significance. Maternal BMI and mean arterial pressure had good significance. PAPP-A and PlGF MoM and serum concentrations were lower when compared to normotensive and had excellent statistical significance. In contrast to singleton pregnancy, uterine artery PI MoM had limited role in preeclampsia prediction (achieved significant P value but, AUC was unsatisfactory). With screen positive rate of 35% risk cut off of 1:75 at false positive rate of 30%

the sensitivity was 75%, specificity was 69%, negative predictive value was 96%, positive predictive value was 21% and detection rate of 70%.

It is unclear why the uterine artery PI is not a significant predictor for preeclampsia in twin pregnancies; this may be due to the difference of uterine artery flow between singleton and twin pregnancies, which needs to be further investigated.

Depending on chorionicity in twin gestation, we did not find any statistically significant different finding among them.

6. Limitations

Sample size has been reduced to bare minimum requirement, due to COVID-19 pandemic and lesser patient attendance. This could also be because many other cases could not be recruited as either they didn't have first trimester screening or did not deliver in this institution.

Based on institutional practise or ACOG/NICE recommendations based on their risk factors, some study participants began therapy for prophylaxis for pre-eclampsia (administration of ecosprin). Because some women receiving treatment might not have developed preeclampsia, this could have affected the study's findings.

Depending on chorionicity in twin gestation, we did not find any statistically significant different finding among them. This could be due to very small number MCDA twins in the study group.

7. Source of Funding

None.

8. Conflict of Interest

None.

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