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First trimester screening for preeclampsia-A prospective observational study

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Abstract

Aims: To evaluate the effectiveness of mean arterial pressure (MAP), pregnancy associated plasma protein-A (PAPP-A) and mean uterine artery doppler pulsatility index (UtPI), individually and in combination, as screening tests to predict the development of preeclampsia, its severity and onset.

Methods: A prospective observational study was done in 800 pregnant women attending the antenatal clinic in a tertiary care centre between 11^{+0} to 13^{+6} weeks. Their MAP, uterine artery doppler and serum PAPP-A were measured and were followed till delivery for the development of preeclampsia, its severity and time of onset. The sensitivity, specificity, positive predictive value and negative predictive value were calculated for these screening tests, individually and in combination. Chi-square test was used to test the statistical significance. A p value <0.05 was considered statistically significant.

Results: A MAP of ≥ 89 mmHg was not strongly associated with the development of preeclampsia. However, mean UtPI ≥ 95^{th} percentile was strongly associated with the development of preeclampsia with specificity of 95.53% and sensitivity of 40.98 %. A value of PAPP-A less than 5th percentile was strongly associated with the development of preeclampsia. By combining MAP and mean UtPI, positive results were associated with the development of preeclampsia with sensitivity of 18.03% and specificity of 99.45 %. With MAP+Mean UtPI+PAPP-A, positive tests results were strongly associated with the development of preeclampsia with specificity of 100% and sensitivity of 11.47%.

Conclusion: The specificity and positive predictive value of the tests were increased with the use of combination of markers than individual markers.

Introduction

Preeclampsia is a hypertensive, multi-system disorder of pregnancy that significantly contributes to maternal and fetal morbidity and mortality.[1] WHO systematically reviews maternal mortality worldwide and in developed countries, 16% of maternal deaths were reported to be due to hypertensive disorders.[2]

The risk of adverse maternal and perinatal outcome increases significantly when preeclampsia develops before 34 weeks gestation.[3] Early identification and prevention is the core tenet of adequate management. The National Institute for Health and Care Excellence (NICE) recommends that women at high risk of preeclampsia must be identified before 13 weeks of gestation and low-dose aspirin must be prescribed until 36 weeks.[4] Screening tests in first trimester consist of a combination of maternal factors and measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UtPI), and serum pregnancy associated plasma protein A (PAPP-A) levels.[5] This study aimed to evaluate the effectiveness of the integrated screening strategies in the first trimester like MAP, UtPI and serum PAPP-A levels for the development of preeclampsia and risk stratification based on those parameters.

Methods

A prospective observational study was conducted involving 800 pregnant women between gestational ages of 11^{+0} to 13^{+6} weeks who attended the antenatal clinic for routine check-up at Kovai Medical Centre and Hospital (tertiary health care centre), Coimbatore, for a period of one year from January to December 2021. Pregnant women aged 40 years or more and those with chronic medical disorders as overt diabetes mellitus, chronic hypertension, renal diseases, antiphospholipid antibody syndrome and gestational trophoblastic diseases were excluded.

Gestational age was determined by the fetal crown-rump length (CRL). A complete maternal history was obtained. Blood pressure was recorded with a sphygmomanometer with the participants in sitting position and their arms supported at the level of heart. It was measured with an adult cuff using the right size for the patient. A series of recordings (minimum of two) were taken until the difference between two consecutive readings was less than 10 mmHg in systolic or 6 mmHg in diastolic blood pressure to obtain the best validity of the measurement. MAP was calculated using the formula:

MAP = Diastolic + 1⁄3 (Systolic - Diastolic).

The participants were subjected to ultrasound nuchal translucency scan between 11^{+0} and 13^{+6} weeks, that included measurement of both UtPI and mean UtPI.

Maternal serum sample was then collected for double marker test that includes both PAPP-A and free beta subunit of human Chorionic Gonadotropin (hCG) hormone.

The participants were followed till delivery. Preeclampsia is diagnosed if the participants had features of proteinuria ≥ 300mg/day, or urine protein:creatinine ratio ≥ 0.3, or persistent dipstick 1+ or renal insufficiency, liver involvement, cerebral symptoms, pulmonary edema, platelet count <100,000/µL, creatinine > 1.1mg/dl or doubling of baseline serum transaminase level twice normal, headache, visual disturbances, convulsions, along with a high BP of 140/90 mm Hg. The development of preeclampsia, severity of preeclampsia and the gestation at onset of preeclampsia were noted. The indicators taken for preeclampsia with severe disease were:

- Diastolic BP ≥ 110mmHg
- Systolic BP ≥ 160 mmHg
- Presence of cerebral symptoms, epigastric pain, oliguria
- Serum creatinine >1.1mg/dl
- Thrombocytopenia <100000/µL
- Marked rise in liver transaminases level
- Presence of fetal growth restriction
- Pulmonary edema.

The data thus collected was entered into excel spread sheet and was double checked. The analysis was done in Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive analysis such as mean, standard deviation, frequencies and percentage were used to express the qualitative data. Chi square test was used to test the significant relationship between the selected factors. All the statistical tests were examined with 5% ($p \leq 0.05$) level of significance.

Results

There were a total of 800 pregnant women enrolled into the study. Table 1 shows the comparison of MAP and development of preeclampsia.

Table 1: Mean arterial blood pressure and development of preeclampsia (N=800).

Mean arterial pressure	Development of preeclampsia (frequency, %)		p value
	Present	Absent	0.153
≥ 89mmHg	26 (10.80%)	215 (89.20%)	
< 89mmHg	35 (6.30%)	524 (93.70%)	

There was no statistical significance between MAP and development and also the severity of preeclampsia.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MAP in detecting preeclampsia were 42.62%, 70.90%, 10.78% and 93.73% respectively.

Pregnancy associated plasma protein A (PAPP-A)

Of 800 cases, 34 (4.25%) cases had PAPP-A value ≤ 5^{th} percentile and 766

(95.75%) cases had PAPP-A value ≥ 10th percentile (Table 2).

Of 34 cases with PAPP-A ≤ 5^{th} percentile, 11(32.4%) cases did not develop preeclampsia, 13 cases (38.2 %) developed mild preeclampsia, 10 (29.4%) cases developed severe preeclampsia. Of 766 cases with PAPP-A value ≥ 10^{th} percentile, 728 (95%) did not develop preeclampsia, 28 (3.6%) had mild preeclampsia, 10 (1.3%) had severe preeclampsia.

Table 2: Association of PAPP-A level and development of preeclampsia (N=800)

PAPP-A range	Development of Preeclampsia (frequency,%)		p value
	Yes	No	< 0.001
≤ 5th percentile	23 (67.6%)	11 (32.4%)	
>5th percentile	38 (5%)	728 (95%)	

Of 15 cases that had developed early onset preeclampsia, nine had PAPP-A value ≤ 5th percentile and six had PAPP-A value ≥ 5th percentile. Similarly among 46 cases that had developed late onset preeclampsia , 14 had PAPP-A value ≤ 5th percentile and 32 had PAPP-A value ≥ 5th percentile.

The sensitivity, specificity, PPV and NPV of PAPP-A in detecting preeclampsia were 37.7%, 98.5%, 67.6% and 95.03% respectively.

Uterine artery doppler screening in first trimester

Of 800 cases, UtPI of 742 (92.8%) cases were <95th percentile while 58 (7.20%) cases were > 95th percentile (Table 3).

Table 3: Association of mean UtPI and development of pre-eclampsia (N=800)

Mean UtPI	Development of preeclampsia (frequency, %)		p value
	Yes	No	< 0.001
≥ 95th percentile	25 (43.1%)	33 (56.9%)	
< 95th percentile	36 (4.9%)	706 (95.1%)	

Out of 58 cases with UtPI ≥95th percentile, 16 (27.6%) had mild preeclampsia and nine (15.5%) had severe preeclampsia. Of 742 cases with UtPI< 95th percentile, 24 (3.2%) had mild preeclampsia and 12 (1.6%) had severe preeclampsia. Of 15 cases who developed early onset preeclampsia, eight had mean UtPI of ≥ 95th percentile and seven had < 95th percentile. Of 46 late onset preeclampsia cases, 17 had mean UtPI ≥ 95th percentile and 29 had < 95 percentile.

The sensitivity, specificity, PPV and NPV of mean UtPI in detecting preeclampsia were 40.98%, 95.53%, 43.10% and 95.15% respectively. Similarly, the sensitivity, specificity, PPV and NPV of MAP and mean UtPI combined in detecting preeclampsia were 18.03%, 99.45%, 73.33%and 93.63% respectively.

Tables 4 and 5 below present the comparison of PAPP-A and UtPI combined for the detection of preeclampsia and its severity.

Table 4: Comparison of PAPP-A and UtPI combined for the development of preeclampsia (N=800).

Development of Preeclampsia	PAPP-A+UtPI (frequency, %)		p value
	Present	Absent	< 0.001
Absent	3 (0.40%)	736 (99.60%)	
Present	16 (26.20%)	45 (73.80%)	

Table 5: Comparison of PAPP-A and UtPI vs severity of preeclampsia (N=800).

Severity of pre-eclampsia	PAPP-A+UtPI (frequency, %)		p-value
	Present	Absent	< 0.001
No preeclampsia	3 (0.30%)	737 (99.70%)	
Mild preeclampsia	10 (25%)	30 (75%)	
Severe preeclampsia	6 (33.30%)	14 (66.70%)	

The sensitivity, specificity, PPV and NPV of PAPP-A and UtPI in detecting preeclampsia were 26.22%, 99.59%, 84.21% and 94.23% respectively.

Table 6: Comparison of MAP + PAPP-A + UtPI and development of preeclampsia (N=800)

Developed Preeclampsia	MAP+UtPI+PAPP-A (frequency, %)		p-value
	Present	Absent	< 0.001
Absent	0 (0%)	739 (100%)	
Present	7 (11.50%)	54 (88.50%)	

Table 6 presents the comparison of combination of all the three markers and development of preeclampsia.

Table 7: Comparison of MAP+UtPI+PAPP-A and severity of preeclampsia

Severity of preeclampsia	MAP+UtPI+PAPP-A (frequency, %)		p-value
	Present	Absent	< 0.001
No preeclampsia	0 (0%)	739 (100%)	
Mild preeclampsia	5 (12.50%)	35 (87.50%)	
Severe preeclampsia	2 (9.50%)	19 (90.50%)	

Five patients developed mild preeclampsia and two developed severepreeclampsia among those who had all the three parameters positive (Table 7). Table 8 shows the comparison of all the three markers combined against gestational age of onset of preeclampsia.

Table 8: Comparison of the markers MAP+UtPI+PAPP-A vs gestational age of preeclampsia development (N=800)

Gestational age of preeclampsia development	MAP+UtPI+PAPP-A (frequency, %)		p-value
	Present	Absent	< 0.001
< 34 weeks	4 (26.60%)	11 (73.33%)	
> 34 weeks	3 (6.52%)	43 (93.47%)	
No preeclampsia	0 (0.00%)	739 (100.00%)	

The sensitivity, specificity, PPV and NPV of the combined markers MAP+PAPP-A+UtPI in detecting preeclampsia were 11.47%, 100%, 100%, and 93.19% respectively.

Discussion

Our study proposed combined screening tests to detect preeclampsia by using mean arterial blood pressure (MAP), maternal serum PAPP-A level and uterine artery doppler in the first trimester and this was the first study to combine these three parameters to predict preeclampsia. We have also studied the sensitivity, specificity, positive and negative predictive values of individual markers as well as combination of markers.

Mean arterial blood pressure:

Out of 241 cases with MAP ≥ 89 mm Hg, 216 (89.60 %) did not develop preeclampsia, 16 (6.6%) cases developed mild preeclampsia and nine (3.7%) cases developed severe preeclampsia. Out of 559 cases with MAP < 89 mm Hg, 523 (93.6%) cases did not develop preeclampsia, 24 (4.30%) had developed mild preeclampsia and 12 (2.1%) had developed severe preeclampsia. There was no significance between MAP and severity of preeclampsia (p-value 0.153), which meant MAP cannot predict the severity of the disease. This was comparable with the study by Miller et al.[9] He concluded that the high quartile MAP was associated with an increased risk of preeclampsia risk but it poorly discriminates between women who will and will not develop the disease.

PAPP-A:

Eleven (29.4%) out of 34 cases did not develop preeclampsia, while 13 (38.20 %) developed mild preeclampsia, and 10 (32.4%) cases developed severe preeclampsia. Of 766 cases with PAPP-A value ≥ 10th percentile, 728 (95.2%) cases did not develop preeclampsia, 28 cases (3.50%) had mild preeclampsia, 10 (1.30%) had severe preeclampsia. Of 15 cases who developed early onset preeclampsia < 34 weeks, 9 cases had PAPP-A value ≤ 5^{th} percentile and 6 cases had PAPP-A value ≥ 5^{th} percentile. Similarly 46 cases who developed late onset preeclampsia, 14 had PAPP-A value ≤ 5^{th} percentile and 32 cases had PAPP-A value ≥ 5^{th} percentile. Leuwan et al. concluded that the pregnancy with PAPP-A levels < 10^{th} percentile was significantly associated with an increased risk of preeclampsia that tended toward early development.[10]

Mean uterine artery Pulsatility Index (UtPI):

Of 15 cases who developed early onset preeclampsia, eight had mean UtPI of ≥ 95^{th} percentile and seven had < 95^{th} percentile. Of 46 late onset preeclampsia cases, 17 had mean UtPI ≥ 95^{th} percentile and 29 cases had < 95^{th} percentile. Veluthar et al. found that the first-trimester uterine artery doppler is a useful

tool for predicting early-onset preeclampsia, as well as other adverse pregnancy outcomes.[11]

Combining MAP + mean UtPI:

Out of 61 cases who developed preeclampsia, combined markers (MAP and UtPI) were positive in 11 cases (18%) and not positive in 50 cases (82%). Of 11 cases (MAP + UtPI positive) seven developed mild preeclampsia, four developed severe preeclampsia. Four had early onset preeclampsia and seven had late onset preeclampsia. The sensitivity, specificity, positive and negative predictive values were 18.03%, 99.45%, 73.33% and 93.63% respectively. We observed in our study that, using combined markers (MAP +mean UtPI) predicts the preeclampsia significantly. Sonek et al. studied the development early onset and late onset preeclampsia in low risk antenatal mothers between 11 to 13^{+6} weeks of gestation by using maternal characteristics (demographic, anthropometric, medical history) maternal biomarkers (MAP, uterine artery Doppler, maternal AFP, PAPP-A, PGF) and estimated placental volume.[6] Based on maternal characteristics, the detection rates for late-onset preeclampsia were 15% and 48% for 5% and 10% false positive rate, while for preeclampsia > 37 weeks gestation the detection rates were 24% and 43%, respectively. They found that the screening for late onset preeclampsia yields a poorer performance.

Combining PAPP-A + mean UtPI:

Among 800 cases, (PAPP-A and UtPI) tests were positive in 19 cases. In that, 16 cases had developed preeclampsia and three did not develop preeclampsia. Of 16 cases, 10 cases had mild preeclampsia and six had severe preeclampsia. Seven cases developed early onset preeclampsia and nine cases late onset preeclampsia. This statistics showed the prediction of preeclampsia and its severity and onset of the disease. There was a significant association of positive tests result with the subsequent development of preeclampsia by combining PAPP-A and mean UtPI. The sensitivity, specificity, positive and negative predictive values were 26.22%, 99.5.9%, 84.21%, and 94.23% respectively.

As reported by Pillas et al. the combination of maternal history with abnormal uterine artery doppler and low PAPP-A level at 11-14 weeks achieved better results than did either test alone in the prediction of pre-eclampsia.[7] Similarly Audibert et al., 2010 proved the association of preeclampsia with abnormal combined markers (PAPP-A, INHIBIN-A, PGF).[8]

Combining PAPP-A, MAP and UtPI:

Out of 61 cases who developed preeclampsia, seven (11.5%) cases were positive for all the three tests, and combined tests were not positive in 54 (88.5%) cases.

Among seven cases, five had mild preeclampsia and two developed severe preeclampsia. We found the severity of the disease with significant p value < 0.001

Of 7 cases, four cases developed early onset preeclampsia and three developed late onset preeclampsia. This was statistically significant with p value < 0.001. If the three markers were combined together, the specificity and positive predictive values of the test reached 100%. Hence there was a strong association between positive tests and subsequent development of preeclampsia. The sensitivity and negative predictive values were 11.47% and 93.17%. Hence from our study, it was concluded that the addition of MAP with PAPP-A and mean UtPI will increase the specificity and positive predictive value of the tests.

Conclusion

The study found MAP of ≥ 89 mmHg was not associated with the development of preeclampsia. Mean UtPI ≥ 95th percentile and PAPP-A less than fifth percentile were strongly associated with the development of preeclampsia.

By combining MAP and mean UtPI, PAPP-A and mean UtPI, positive results were associated with the development of preeclampsia. With PAPP-A +MAP + Mean UtPI, positive tests results were strongly associated with the development of preeclampsia compared to doing screening test alone with specificity of 100% and sensitivity of 11.47%. In our study, we observed that the specificity and positive predictive value of the tests increase, if combined markers are used than individual markers.

Limitations

The study was limited by relatively small number of sample size, especially for early onset cases. Only three parameters for predicting preeclampsia were used. Addition of other maternal serum biomarkers may improve the strength of the study.

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References

1. Bell MJ. A historical overview of preeclampsia-eclampsia. Journal of Obstetric, Gynecologic & Neonatal Nursing. 2010 Sep 1;39(5):510-8. DOI: 10.1111/j.1552-6909.2010.01172.x
2. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006 Apr 1;367(9516):1066–74. DOI 10.1016/S0140-6736(06)68397-9
3. Sajith M, Nimbargi V, Modi A, Sumariya R, Pawar A. Incidence of pregnancy induced hypertension and prescription pattern of antihypertensive drugs in pregnancy. Int J Pharma Sci Res. 2014;23:4. Available from: Incidence of pregnancy induced hypertension and prescription pattern of antihypertensive drugs in pregnancy (ijpsr.info)

4. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol. 2014 Oct;124(4):771–81. DOI: 10.1097/AOG.0000000000000472

5. Bartsch E, Medcalf KE, Park AL, Ray JG; High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016 Apr 19;353:i1753. DOI: 10.1136/bmj.i1753. PMID: 27094586; PMCID: PMC4837230.

6. Sonek J, Krantz D, Carmichael J, Downing C, Jessup K, Haidar Z, et al. First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume. Am J Obstet Gynecol. 2018;218(1):126.e1-126.e13. DOI 10.1016/j.ajog.2017.10.024

7. Pilalis A, Souka AP, Antsaklis P, Daskalakis G, Papantoniou N, Mesogitis S et al. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler and PAPP-A at 11-14 weeks' gestation. Ultrasound Obstet Gynecol. 2007 Feb;29(2):135-40. doi: 10.1002/uog.3881. PMID: 17221926.

8. Audibert F, Boucoiran I, An N, Aleksandrov N, Delvin E, Bujold E, et al. Screening for preeclampsia using first-trimester serum markers and uterine artery Doppler in nulliparous women. Am J Obstet Gynecol. 2010 Oct;203(4):383.e1-8. DOI: 10.1016/j.ajogi.2010.06.014

9. Miller RS, Rudra CB, Williams MA. First-trimester mean arterial pressure and risk of preeclampsia. Am J Hypertens. 2007 May;20(5):573–8. DOI: Luewan S, Teja-Intr M, Sirichotiyakul S, Tongsong T. Low maternal serum pregnancy-associated plasma protein-A as a risk factor of preeclampsia. Singapore Med J. 2018 Jan;59(1):55-59. doi: 10.11622/smedj.2017034. Epub 2017 Apr 28. PMID: 28451695; PMCID: PMC5778261.

10. Velauthar L, Plana MN, Kalidindi M, Zamora J, Thilaganathan B, Illanes SE, et al. First-trimester uterine artery doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. Ultrasound Obstet Gynecol. 2014 May;43(5):500–7. DOI: 10.1002/uog.13275