



## THE IMPACT OF UTERINE ARTERY DOPPLER ASSESSMENT AT 11-13+6 WEEKS GESTATIONAL AGE ON STRATIFICATION OF EARLY ONSET PREECLAMPSIA AT A TERTIARY CARE TEACHING HOSPITAL IN NORTH INDIA

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### ABSTRACT

• **Introduction:** Clinical history alone that is used to stratify risk to develop preterm preeclampsia in pregnant women may overestimate the number of pregnant women that need preventative therapy with low dose aspirin. Integration of mean arterial blood pressure (MAP) and mean uterine artery pulsatility index (mean UtA PI) Doppler studies with clinical history can reduce the proportion of women identified at high risk and consequently started on low dose aspirin.

• **Aim:** The purpose of this study was to quantify the difference in the proportion of women identified at high risk for preterm PE using a combined screening model and clinical history alone model.

• **Materials and methods:** A cross sectional study of pregnant women screened between 11-13+6 gestational weeks included clinical history, mean arterial blood pressure measurements (MAP) and mean uterine artery pulsatility index (Mean UtA PI) using fetal Doppler assessment for all enrolled women. An individualized risk for preterm preeclampsia based on clinical history alone and risk based on clinical history combined with MAP and Mean UtA PI was determined using a cutoff of 1 in 150 and the Fetal Medicine Foundation online calculator. The difference in the proportion of high-risk women using these two strategies was determined and a pairwise correlation test to correlate the two risk scores.

• **Results:** The study included 49 pregnant women screened between 11-13+6 gestational weeks from March to September 2025. Screening by clinical history alone identified 36 (73.47%) first trimester women at high risk compared to 19 (38.78%) pregnant women identified at high risk using the combined screening model ( $p=0.0006$ ). The pairwise correlation (0.28) of risk scores by history alone and the combined screening model was poor.

**Conclusions:** The integration of MAP and Mean UtA PI with clinical history will significantly reduce the number of women identified at high risk for preterm PE and consequently reduce the number of women that must be provided low dose aspirin and need more frequent surveillance. This will reduce the strain on health care infrastructure and economic strain on patients

**Keywords:** Preeclampsia, uterine artery Pulsatility index, Mean arterial pressure

## •INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are a major cause of obstetric morbidity and affects nearly 10% of pregnant women worldwide.<sup>1</sup>Preeclampsia (PE) is one of the disorders that constitute HDP with an estimated global pooled incidence that varies between 2 and 5%.<sup>2,3</sup>PE is a major contributor to the magnitude of severe acute maternal morbidity (SAMM), near miss, maternal mortality, perinatal mortality, fetal growth restriction and adverse perinatal outcomes.<sup>3</sup>Globally, 76,000 women and 500,000 babies die each year because of PE complicating pregnancy. Pregnant women in low-resource countries are at a higher risk of developing PE compared to those in high-resource countries.<sup>3</sup>The large variation in the reported incidence and outcomes of PE between countries and even within countries maybe attributable to true population differences, differences in healthcare provision and healthcare systems, and differences in data acquisition and reporting.

PE is a multifactorial disease that can affect multiple organ systems in the body. Several factors can interact to cause the disease including defective placentation, oxidative stress, autoimmunity, platelet and thrombin activation, intravascular inflammation, endothelial dysfunction, imbalance in angiogenesis and maternal cardiac maladaptation.<sup>4,5</sup>The current knowledge of the pathogenesis of PE suggests a two-stage process.<sup>3</sup>The first stage caused by shallow invasion of the trophoblast results in inadequate remodelling of the spiral arteries. The first stage leads to the second stage that involves the maternal response to endothelial dysfunction and imbalance between angiogenic and anti-angiogenic factors, and result in the clinical features of the disorder.

Defective placental invasion is associated strongly with most cases of early and severe PE.<sup>4</sup>Defective placentation is however less important for the development of PE that manifests later in pregnancy or after 34 gestational weeks. Compared with pregnancies affected by early-onset disease, placentae have a significantly lower frequency of histological abnormalities in those complicated with PE at or near term,<sup>6</sup> and maternal factors have a relatively greater significance.<sup>4</sup>The differences between early- and late-onset PE are also seen in risk factors, maternal vascular responsiveness, screening performance and prevention effectiveness.<sup>7-10</sup>

Several definitions have been used to describe PE, which has hampered our understanding of the pathogenesis, risk factors, course, and outcomes of PE. PE was previously defined as the new onset of hypertension with significant proteinuria after 20 weeks' gestation. Currently, the International Society for the Study of Hypertension in Pregnancy (ISSHP) definition is commonly used in clinical and research settings to define PE. According to the ISSHP, PE is defined<sup>11</sup> as systolic blood pressure at  $\geq 140$  mmHg and/or the diastolic blood pressure at  $\geq 90$  mmHg on at least two occasions measured four hours apart in previously normotensive women and is accompanied by  $\geq 1$  of the following new-onset conditions at or after 20 weeks' gestation:

- proteinuria (i.e.,  $\geq 30$  mg/mol protein: creatinine ratio;  $\geq 300$  mg/24hr; or  $\geq 2+$  dipstick);
- evidence of other maternal organ dysfunction, including: acute kidney injury (creatinine  $\geq 90$   $\mu$ mol/L; 1 mg/dL), liver involvement (elevated transaminases, e.g., alanine aminotransferase or aspartate aminotransferase  $>40$  IU/L) with or without right upper quadrant or epigastric abdominal pain, neurological complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata), or hematological complications (thrombocytopenia—platelet count  $<150000/\mu$ L, disseminated intravascular coagulation, hemolysis); or
- uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth).

Several studies have explored the potential to predict the onset of PE in pregnant women using clinical, ultrasound and laboratory parameters. These include the study of uterine artery Doppler parameters,<sup>2</sup> measurement of angiogenic factors such as soluble endoglin, PlGF, sFlt-1, and sFlt-1/PlGF ratio<sup>12</sup> and factors such as plasma pregnancy-associated plasma protein A, placental protein

13, homocysteine, asymmetrical dimethylarginine, uric acid and leptin, urinary albumin, or calcium.<sup>13-17</sup>

Maternal characteristics that are most strongly associated with an increased likelihood of preeclampsia include the above listed factors and underlying renal disease or multiple pregnancies. Other factors less strongly associated with preeclampsia include, but are not limited to advanced maternal age,<sup>18</sup> family history of preeclampsia,<sup>19,20</sup> Short duration of sexual relationship (<6 months) before the pregnancy,<sup>21,22</sup> primiparity, primipaternity and an interpregnancy interval >5 years,<sup>23,24</sup> and chronic kidney disease and connective tissue diseases.<sup>25</sup>

A large systematic review reported that parity, preeclampsia history, race, chronic hypertension, and conception method had an area under the curve 0.76 for predicting early onset preeclampsia and that specialized tests can further improve the discriminative ability.<sup>26</sup> Improvements in discrimination were more modest for models predicting any preeclampsia and late-onset preeclampsia compared to models for prediction of early onset preeclampsia.

Zymeri NA, et al<sup>27</sup> described the protocols of assessment for mean arterial pressure at 11-13 weeks gestation. They compared the performance of screening for PE by different combinations of MAP to the protocol of the National Heart Foundation of Australia (NHFA). The area under the receiver operating characteristic curve (AUROC) for prediction of PE by MAP as recommended by the NHFA protocol was 0.773 (95% CI 0.768-0.778). This AUROC was not significantly different from the AUROC obtained by the average MAP of the first three measurements from one arm (0.765, 95% CI 0.760-0.771) or the average of the first (0.766, 95% CI 0.760-0.771), the first two (0.771, 95% CI 0.766-0.777), or the first three measurements from the two arms (0.773, 95% CI 0.768-0.778). They concluded that the performance of screening for PE by taking the average of a minimum of two measurements from both arms is comparable to the NHFA protocol.

O'Gorman, et al,<sup>28</sup> reported that the values of uterine artery pulsatility index and mean arterial pressure were increased, and the values of serum pregnancy-associated plasma protein-A and placental growth factor were decreased in pregnant women with preeclampsia. For all biomarkers, the deviation from normal was greater for early than late preeclampsia; therefore, the performance of screening was related inversely to the gestational age at which delivery became necessary for maternal and/or fetal indications. Combined screening by maternal factors, uterine artery pulsatility index, mean arterial pressure, and placental growth factor predicted 75% (95% confidence interval, 70-80%) of preterm-preeclampsia and 47% (95% confidence interval, 44-51%) of term-preeclampsia, at a false-positive rate of 10%; inclusion of pregnancy-associated plasma protein-A did not improve the performance of screening. Such detection rates are superior to the respective values of 49% (95% confidence interval, 43-55%) and 38% (34-41%) that were achieved by screening with maternal factors alone.

Sotiriadis A, et al recommended that both transabdominal or transvaginal routes may be used for Doppler of uterine arteries in the first trimester.<sup>2</sup> The preferred application is the Transabdominal route because most screening methods used this approach. The mean of both uterine arteries pulsatility index (PI) is preferred for Preeclampsia screening. They observed PI of uterine artery >90th centile will detect 48% of females who are at risk to evolve into early PE & with a 10% screen-positive rate, there will be 26% of people who progress to any PE. They suggested that a combination of maternal clinical variables, mean PI of uterine arteries Doppler, mean arterial Pressure, and placental growth factor level at 11 to 14 weeks is the most reliable screening tool for determining preeclampsia risk in expecting women.

O'Gorman, et al<sup>28</sup> reported that the detection rates for preterm and term preeclampsia were inferior using National Institute for Health and Care Excellence (NICE) or American College of Obstetrics

and Gynaecology (ACOG) clinical criteria alone to first trimester screening using a multivariable approach (that included maternal risk factors, BP, maternal plasma pregnancy-associated plasma protein A and PlGF, and uterine artery Doppler). At a screen-positive rate of 10%, 370 women would have to be screened, and the 37 identified as being at high risk of preeclampsia treated with 150 mg/d of aspirin to prevent 1 case of preterm preeclampsia. Importantly, the vast majority ( $\approx 80\%$ ) of screen-positive women did not have strong clinical risk factors for preeclampsia.

Preventative therapy or therapy to prevent the onset of PE in high risk pregnant women is available using low dose aspirin initiated early in pregnancy. The ASPRE study (Aspirin Versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia), included 822 expectant females in the placebo group and 798 females in the aspirin group. The ASPRE examination combined maternal clinical factors mean arterial pressure, mean PI of the uterine arteries, and maternal biochemical indicators in pregnant women in the first trimester. They calculated the PE risk and women with a risk of  $>1$  in 100 were included in the aspirin trial (150mg/day) versus placebo from 11-14 to 36 weeks of gestation. Preeclampsia affected 13 patients (1.6%) and 35 (4.3%) in the aspirin and placebo group. All participants adhered to the aspirin intake, and they inferred that lower dosage preventive aspirin therapy in higher-risk females was more effective in comparison to placebo to decrease the prevalence of PE.<sup>10</sup> The ASPRE study has demonstrated that the use of 150mg aspirin at night in women deemed to be high risk for preterm preeclampsia on the basis of screening with maternal factors, and Doppler and maternal PlGF reduced the incidence of preterm preeclampsia from 4.3% to 1.6% in the aspirin group. An important finding in the ASPRE was confirmation that aspirin at a dose of 150 mg at night conferred no greater risk to pregnant women (or their newborns) than placebo.<sup>10</sup>

An estimated 30 million women become pregnant every year in India. India was a significant contributor to the poor perinatal statistics worldwide with high maternal, neonatal, and infant mortality rates and stillbirth rates. There has been considerable progress in the reduction of adverse perinatal events with significant reductions in the maternal rates, neonatal, infant and perinatal mortality rates although more rapid reduction is needed to achieve the sustainable development goals targets. PE is a major contributor to the poor maternal healthcare statistics in India. The national health portal of India reports a pooled incidence of 8-10% PE in India. If we convert these to absolute numbers, an estimated 2.4 to 3 million women may develop PE in India every year placing a substantial burden on the healthcare infrastructure of the country in the short and long term.

The Indian Radiological and Imaging Association (IRIA) started a nationwide program -Samrakshan- that aimed to reduce the perinatal mortality in India through an integrated approach. Samrakshan focused on two priority areas, preeclampsia (PE) and fetal growth restriction (FGR). An interim analysis done two years after initiation of the program reported that fetal Doppler integrated antenatal ultrasound studies led to a significant reduction in preterm PE rates from 9.85% to 2.76%, reduction in preterm birth rates from 29.54% to 19.28%, and a significant improvement in mean birth weights.<sup>30</sup> The neonatal mortality rate was 9.86/1,000 live births, perinatal mortality rate was 18.97/1,000 childbirths, and maternal mortality was 58/100,000 live births compared with 29.5, 36, and 113, respectively in 2016.<sup>30</sup> The perinatal, neonatal, and maternal mortality rates are significantly better than the targets for 2030 set by the Sustainable Development Goals-3. The Samrakshan program reported that first trimester protocol-based approach had a high specificity (90.4%, 95% CI: 89.4%, 91.2%) and negative predictive value (98.1%, 95% CI: 97.6%, 99%) for preterm PE.<sup>31</sup> The odds ratio and positive likelihood ratio for preterm PE were 16.7 (95% CI: 12.3, 22.6) and 6.64 (95% CI: 5.77, 7.63), respectively.<sup>31</sup> The area under the receiver operator characteristic (AUROC) curve was 0.76 (95% CI: 0.74, 0.82). Preterm PE developed in only 1.90% of women identified as low risk for preterm PE. Preterm PE did not develop in 75.6% of the women who were at high risk for preterm PE and were recommended low dose aspirin.<sup>31</sup>

It is anticipated that the number of women identified at high risk for the development of preterm PE will reduce as more specialized tests are added as these tests will improve the accuracy of the protocols and reduce the number of false positives. Tousty P, et al reported that between 21% and 29% of women at a low risk of preterm PE could be given acetylsalicylic acid if the screening test that was used did not include PlGF. Biochemical tests improve the predictive ability but are currently not feasible on a large scale in India due to several reasons including affordability, availability and accessibility to the tests, the turnaround times for the results and suboptimal compliance with recommended antenatal follow-up schedules. A model that includes mean arterial blood pressure and mean uterine artery PI measurements can address some of these limitations as it can be done at the same time as the routine 11–14-week antenatal ultrasound test. Fetal Doppler studies are non-invasive, relatively painless and results can be interpreted and reported in real time. However, the combined screening approach adds to patient and hospital costs compared to a clinical history-based approach. There is not much information on the impact of utilizing this combined screening approach compared to the current strategy of risk stratification based on clinical history alone. This study was aimed to address this gap in the literature and to determine if the shift from a clinical history to a combined screening approach will reduce the number of women labelled as high risk for preterm PE and started on low dose aspirin at the study institute.

### 3. HYPOTHESIS AND OBJECTIVES

#### **Hypothesis:**

The use of a combined screening model that includes mean arterial blood pressure and mean uterine artery pulsatility index measurements at 11-13+6 gestational weeks will reduce the proportion of pregnant women identified at high risk for preterm preeclampsia in comparison to a model that is based on clinical history alone.

#### **Objectives:**

- **General objective:** To compare the proportion of pregnant women identified at high risk for preterm preeclampsia using a clinical history protocol alone and a combined screening protocol including mean arterial blood pressure and mean uterine artery pulsatility index at 11-13+6 gestational weeks of pregnancy.

- **Specific objectives:**

1. Ascertain and collect relevant clinical information at 11-13+6 gestational weeks to stratify risk for preterm preeclampsia.
2. Measure the mean arterial blood pressure at 11-13+6 gestational weeks.
3. Measure the mean uterine artery pulsatility index at 11-13+6 gestational weeks by Transvaginal Sonography.
4. Ascertain risk for preterm preeclampsia based on clinical history and combined screening and determine proportion of high-risk women identified using both models using an online calculator of the Fetal Medicine Foundation.
5. Recommend low dose aspirin preventative therapy for pregnant women identified at high risk for preterm preeclampsia.

### 4. MATERIALS AND METHODS

The study protocol that utilized a cross sectional study design was approved by the Institutional Review Board of the study institute (Rajshree Medical Research Institute, Bareilly, North India)<sup>41</sup> and adhered to the tenets of the Declaration of Helsinki. The study was conducted between March 2025 and September 2025. Pregnant women who attended the Radiology department at the study institute for antenatal ultrasound assessments at 11-13+6 gestational weeks were considered eligible for enrolment into the study. The study included pregnant women with an ultrasound confirmed dating of pregnancy as 11-13+6 gestational weeks, with a singleton or twin live fetus and provided informed

consent for participation in the study. The study excluded pregnant women who did not provide informed consent, with an unviable fetus, with gestational age either less than 11 weeks or more than 13<sup>+6</sup> weeks, multifetal pregnancy with more than two fetuses, and in whom a fetal abnormality was detected on ultrasound assessment. Consecutive pregnant women were enrolled in the study based on the inclusion and exclusion criteria. Each enrolled and eligible woman was assigned a unique alphanumeric study ID to anonymize the identity of the woman.

A detailed clinical history was obtained from all pregnant women enrolled in the study. This included the maternal age at assessment, the type of conception, current and past medical & obstetric history, interpregnancy interval if the woman was multiparous, details of the previous pregnancy if the woman was multiparous, and personal risk behaviours like smoking. Information on pertinent risk factors for preeclampsia was collected ascertained based on the American College of Obstetrics and Gynaecology (ACOG) practice bulletin.

At the study institute, preeclampsia was adapted from the ISSHP definition<sup>11</sup> as

- the presence of a systolic blood pressure more than 140mm Hg and diastolic blood pressure more than 90mmHg on two separate assessments in a previously normotensive woman in the absence of proteinuria and/or maternal acute kidney injury (AKI), liver dysfunction, neurological features, hemolysis or thrombocytopenia in a pregnant woman after 20 gestational weeks, or
- Gestational hypertension with proteinuria (300mg or over) in 24-hour urine sample, or two separate sample of dipstick showing ++ proteinuria, or proteinuria in a catheter collection of urine sample if 24 hour urine sample was not available, in a pregnant woman after 20 gestational weeks
- Significant proteinuria after 20 gestational weeks in a pregnant woman with chronic hypertension

The mean arterial blood pressure was measured for each enrolled pregnant woman as per the recommended protocol.<sup>27</sup> The blood pressure was measured in a quiet room with the woman seated comfortably in a chair with both feet flat on the floor and arms resting on a table in front of her. Calibrated digital blood pressure instruments with a normal or large arm cuff (as appropriate) was used for the measurement. The blood pressure was measured simultaneously in both upper arms and repeated after an interval of 1-2 minutes. The systolic and diastolic measurements of both assessments were documented and entered the fetal medicine online calculator to derive the mean arterial blood pressure. The normal range of mean arterial pressure is 60-100mm of Hg.

The antenatal ultrasound assessment at 11-13+6 gestational weeks included dating of pregnancy, measurement of the crown rump length, confirmation of fetal viability and number of fetuses, and assessment for presence or risk factors for fetal abnormalities. Pregnant women with a crown rump length of the fetus that was <45mm or >84mm were excluded from further inclusion in the study.

Uterine artery Doppler study was done using a transvaginal approach to determine the mean uterine artery pulsatility index (PI).<sup>2</sup> The woman was placed in a lithotomy position, with an empty bladder and a transvaginal probe was used to obtain a sagittal view of the cervix. The probe was located at the anterior fornix and then moved laterally until the paracervical vascular plexus was seen. The uterine artery was identified at the levels of the internal os and measurements were taken with an angle of insonation of <30°. The Doppler wave form was obtained and a uterine artery peak systolic velocity >60cm/s was considered to verify that the uterine artery was being examined and to differentiate it from cervico-vaginal or arcuate arteries. The pulsatility index (PI) was measured when three identical waveforms were obtained. The right and left mean uterine artery PI readings were entered into an online calculator of the Fetal Medicine Foundation to determine the mean uterine artery PI. Table /fig 1, Table/fig 2

The clinical information, mean arterial blood pressure and mean uterine artery pulsatility index was entered in the Fetal Medicine Foundation online calculator at <https://fetalmedicine.org/research/assess/preeclampsia/first-trimester>

The FMF calculator uses a competing risk Bayesian algorithm to determine the risk for preeclampsia based on clinical history alone and after incorporating mean arterial blood pressure and mean uterine artery pulsatility index measurements. A cutoff of 1 in 150 was used to stratify the risk for preterm preeclampsia as high or low risk. Pregnant women identified at high risk for preterm preeclampsia based on the combined screening model and a 1 in 150 cutoff were recommended to start 150 mg low dose aspirin, once daily at bedtime, till 36 weeks of pregnancy or development of preterm preeclampsia or childbirth, whichever was earlier, and in consultation with their managing obstetrician.

The data used for the for the individualized risk assessment was entered into an MS Excel spreadsheet after anonymizing the identity of the woman<sup>40</sup>. The data was subsequently exported to STATA v11.0 (STATA Corp, College Station, Tx, USA) statistical software for analysis. The distribution of parameters was expressed as a mean (SD) for continuous variables and proportions for categorical variables. The proportion of women identified at high risk for preterm preeclampsia by history alone and by using clinical History with mean arterial pressure and mean PI of uterine arteries was estimated and compared using a test of proportions. The proportion of women recommended low-dose aspirin was ascertained. A pairwise correlation test was used to check for the correlation of the risk values of each woman obtained using clinical history alone and the combined model that included mean arterial blood pressure and mean uterine artery PI.

## 5. RESULTS

Forty-Nine women were screened in the first trimester of pregnancy as part of this study. The mean age (SD) of women was 29.59 (3.72) years and 31 (63.27%) women were screened at 12 to 13 gestational weeks. All the screened women were of Asian Indian ethnicity. None of the women gave a history of smoking or family history of pre-eclampsia. None of the multiparous women gave a history of preeclampsia in the previous pregnancy. The clinical and demographic details of these 49 women are presented in Table/Fig-3.

Statistics: When we used a cutoff criterion of 1 in 150 to stratify risk for preterm preeclampsia, screening by clinical history alone identified 36 (73.47%) first trimester women at high risk compared to 19 (38.78%) pregnant women identified at high risk using the combined screening model ( $p=0.0006$ ). The pairwise correlation (0.28) was poor when the risk assessment values were compared for the risk assessment by history alone and using the combined screening model. Low dose aspirin 150mg at bedtime was initiated for the 19 high risk pregnant women identified using the combined model.

Table/Fig-3: Clinical and Demographic details of the 49 pregnant women screened in the study

| Parameter                                  |               |
|--------------------------------------------|---------------|
| Mean Age (SD) years                        | 29.59 (3.72)  |
| Mean Body Mass Index (SD)                  | 26.31 (4.82)  |
| Lean (Body Mass Index <18.5) (n,%)         | 3, 6.12%      |
| Normal (Body Mass Index 18.5-24.9) (n,%)   | 14, 28.57%    |
| Overweight (Body Mass Index 25-29.9) (n,%) | 18, 36.73%    |
| Obese (Body Mass Index ≥30) (n,%)          | 14, 28.57%    |
| Mean (SD) Maternal Height in Centimeters   | 155.61 (7.08) |
| Mean (SD) Maternal Weight in Kilograms     | 63.76 (12.51) |
| Mean (SD) Crown-Rump Length                | 61.83 (7.86)  |
| Singleton Pregnancies (n,%)                | 46, 93.88%    |
| Nulliparous (n,%)                          | 31, 63.27%    |

|                                            |               |
|--------------------------------------------|---------------|
| Spontaneous or Natural Conception (n,%)    | 45,91.84%     |
| Chronic Hypertension (n,%)                 | 1, 2.04%      |
| Type 2 Diabetes Mellitus (n,%)             | 4, 8.16%      |
| Mean (SD) interpregnancy interval in years | 3.1 (2.48)    |
| Mean (SD) mean arterial blood pressure     | 85.35 (10.59) |
| Mean (SD) Uterine Artery Pulsatility Index | 1.57 (0.50)   |

## 6. DISCUSSION

The study results indicate that the proportion of women identified at high risk for preterm PE and consequently started on low dose aspirin reduces significantly when a combined screening model integrating MAP and mean UtA PI with clinical criteria is used at 11-13+6 gestational weeks compared to a clinical history alone model. The correlation of risk scores obtained in the combined screening model and the clinical history alone model was poor.

The traditional approach to screening for pre-eclampsia (PE) is to identify risk factors from maternal demographic characteristics and medical history (maternal factors).<sup>28</sup>In the USA, according to the American College of Obstetricians and Gynecologists (ACOG), taking a medical history to evaluate for risk factors is currently the best and only recommended screening approach for PE. Risk factors include nulliparity, age > 40 years, BMI  $\geq 30$  kg/m<sup>2</sup>, conception by in-vitro fertilization, history of previous pregnancy with PE, family history of PE, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia.<sup>32</sup>This approach essentially considers each risk factor as a separate screening test, with additive detection rate (DR) and screen-positive rate.

An alternative approach to screening, developed by The Fetal Medicine Foundation (FMF), allows estimation of individual patient-specific risks of PE requiring delivery before a specified gestation, with the use of Bayes' theorem to combine the a-priori risk from maternal factors, derived by a multivariable logistic model, with the results of various combinations of biophysical and biochemical measurements.<sup>9,33</sup> A recent multicentre study in 8775 singleton pregnancies confirmed the validity of the algorithm and reported DRs of 100% (95% CI, 80–100%), 75% (95% CI, 62–85%) and 43% (95% CI, 35–50%) for PE delivering < 32, < 37 and  $\geq 37$  weeks, respectively, at a 10% FPR.<sup>34</sup>These studies suggest that an improved algorithm to stratify risk with the incorporation of specialized tests will reduce the proportion of false positive pregnant women identified at high risk. A recent study reported that the detection rate of PE with delivery at <32 weeks, <37 weeks and  $\geq 37$  weeks was 53% (95% CI 28-77), 41 % (95% CI 28-54) and 37% (95% CI 30-45) respectively.<sup>28</sup> The integration of MAP and mean UtA with clinical criteria improved the detection rate of PE with delivery at <32 weeks, < 37 weeks and  $\geq 37$  weeks to 94% (95% CI 74-100), 71% (95% CI 58-82) and 41% (95% CI 34-49) respectively.

Tousty P, et al,<sup>35</sup> assessed the detectability of women at risk of developing early onset PE depending on the algorithm used. They studied 801 patients and divided the patients into four groups based on a risk calculation algorithm: 1) screening based on UtA PI, MAP, and PlGF; 2) screening based on UtA PI, MAP, PAPP-A, and PlGF; 3) screening based on UtA PI, MAP, and PAPP-A; and 4) screening based on UtA PI and MAP. They selected patients within groups where the risk of early onset PE was >1 : 150 and compared the UtA PI, MAP, PAPP-A, and PlGF values. They reported that for the cut-off point >1 : 150, 86 women were at an increased risk of early onset PE using algorithm 1. Of these 86 patients, 83 (96%) were identified using algorithm 2, 62 (72%) using algorithm 3, and 60 (69%) using algorithm 4. They also found that between 21% and 29% of women at a low risk of early onset PE could be given acetylsalicylic acid if a screening test was used that did not account for PlGF.<sup>35</sup>

The improved detection rates of pregnant women at high risk for preterm PE or early onset PE will reduce the number of low-risk pregnant women started on low dose aspirin. The results of our study are consistent with the evidence from these studies.<sup>28,35</sup>

## Limitations

The inability to follow up the screened pregnant women to identify the false positive and false negative rates, and to determine the incidence of preterm PE is a limitation of the study. However, this was a pragmatic limitation due to the constraints of time to conduct the study. We aim to continue the study further to address this limitation. The study population is derived from a single center and will not be representative of the general population of pregnant women in India or even the north Indian state, which is one of the largest states in India, where the study institute is located. The constraints of time for the study also limited our sample size (n=49). The strength of the studies include the fact that a single trained senior radiologist performed all ultrasound and Doppler assessments, individualized risk assessments were ascertained using a validated algorithm, and protocol based assessments were followed.

### **Implications for Practice**

The new pyramid of pregnancy care that includes assessment of risk at 11–13 weeks' gestation aims to identify pregnancies at high risk of developing PE and, through pharmacological intervention with such medications as low-dose aspirin, reduce the incidence of these complications.<sup>36-39</sup> Administration of low-dose aspirin from the first-trimester to those at high risk is effective in prevention of preterm, rather than term, PE, and the use of the combined screening methods are superior to those clinical criteria in identifying the group of pregnancies that could benefit from such therapy. According to FMF, about 10% of the pregnant population would receive low-dose aspirin and this population would contain 75% of those that will develop preterm PE if selection of the high-risk group was based on the FMF algorithm. In the case of the ACOG recommendations, 0.2% of the population would receive aspirin and only 5% of cases of preterm PE that would potentially benefit from such therapy would be targeted.

Recording of maternal history and measurement of blood pressure are universally carried out as part of routine pregnancy care; measurement of MAP requires adherence to a protocol but can be undertaken by healthcare assistants after minimal training, using inexpensive equipment and taking a few minutes to perform. Measurement of UtA-PI requires specific training by fetal radiologists in India and quality assurance of their results; however, this test can be undertaken within a few minutes by the same radiologist and machine as part of the routine first-trimester scan.

The results of our study suggest that a shift towards combined screening will benefit the pregnant women presenting to the study institute compared to screening based on clinical criteria alone. This shift can help reduce the unnecessary expenses related to low dose aspirin and follow up visits for the pregnant women and reduce the economic, human resource and infrastructure strain on the healthcare setting.

### **7. CONCLUSIONS**

- The correlation between the individualized risk scores obtained in the clinical history model and the combined model that used clinical history, MAP and mean UtA PI was poor.
- The combined model significantly reduced the proportion of pregnant women considered at high risk for preterm PE to 38.78% from the 73.47% identified using clinical history alone.
- This significant reduction in the proportion of high risk women will translate to a significant number of low risk women not being subjected unnecessarily to intervention with low dose aspirin.
- The reduction in labelling women as high risk will also reduce the need to schedule more frequent follow up visits and more intense surveillance leading to financial benefits for the patient and economic, human resource and infrastructure benefits for the healthcare system.
- The results of our study indicate that a combined screening model is more optimal than a clinical history alone model at the study institute and calls for a change of current practice patterns at the study institute.

## 8. BIBLIOGRAPHICAL REFERENCES

1. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009; 33: 130–137.
2. Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A, et al; ISUOG CSC Pre-eclampsia Task Force. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. *Ultrasound Obstet Gynecol.* 2019;53(1):7-22. doi: 10.1002/uog.20105. Epub 2018 Oct 15. PMID: 30320479.
3. Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet.* 2019 May;145 Suppl 1(Suppl 1):1-33. doi: 10.1002/ijgo.12802.
4. Chaiworapongsa T, Chaemsaitong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol* 2014; 10: 466–480.
5. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular implications in preeclampsia: an overview. *Circulation* 2014; 130: 703–714.
6. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. *Fetal Diagn Ther* 2014; 36: 117–128.
7. Llurba E, Carreras E, Gratacós E, Juan M, Astor J, Vives A, et al. Maternal history and uterine artery Doppler in the assessment of risk for development of early- and late-onset preeclampsia and intrauterine growth restriction. *Obstet Gynecol Int.* 2009;2009:275613. doi: 10.1155/2009/275613.
8. Stergiotou I, Crispi F, Valenzuela-Alcaraz B, Bijnsens B, Gratacos E. Patterns of maternal vascular remodeling and responsiveness in early- versus late-onset preeclampsia. *Am J Obstet Gynecol* 2013; 209: 558.e1–14.
9. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11–13 weeks gestation. *Am J Obstet Gynecol* 2016; 214: 103.e1–12.
10. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017; 377: 613–622.
11. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension.* 2018;72(1):24-43. doi: 10.1161/HYPERTENSIONAHA.117.10803.
12. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med.* 2004;350:672–683. doi: 10.1056/NEJMoa031884
13. Baweja S, Kent A, Masterson R, Roberts S, McMahon LP. Prediction of pre-eclampsia in early pregnancy by estimating the spot urinary albumin: creatinine ratio using high-performance liquid chromatography. *BJOG.* 2011;118:1126–1132. doi: 10.1111/j.1471-0528.2011.02960.x.
14. Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, Bossuyt PM, van der Post JA, von Dadelszen P, et al; EBM CONNECT Collaboration. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. *BJOG.* 2012;119:778–787. doi: 10.1111/j.1471-0528.2012.03311.x.
15. Di Lorenzo G, Ceccarello M, Cecotti V, Ronfani L, Monasta L, Vecchi Brumatti L, et al. First trimester maternal serum PIGF, free  $\beta$ -hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of preeclampsia. *Placenta.* 2012;33:495–501. doi: 10.1016/j.placenta.2012.03.003.
16. Myatt L, Clifton RG, Roberts JM, Spong CY, Hauth JC, Varner MW, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal

- Medicine Units (MFMU) Network. First-trimester prediction of preeclampsia in nulliparous women at low risk. *Obstet Gynecol.* 2012;119:1234–1242. doi: 10.1097/AOG.0b013e3182571669.
17. Masoura S, Kalogiannidis IA, Gitas G, Goutsoulis A, Koiou E, Athanasiadis A, et al. Biomarkers in pre-eclampsia: a novel approach to early detection of the disease. *J ObstetGynaecol.* 2012;32:609–616.
18. 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;353:i1753. doi: 10.1136/bmj.i1753.
19. North RA, McCowan LM, Dekker GA, Poston L, Chan EH, Stewart AW, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ.* 2011;342:d1875.
20. Parra-Cordero M, Rodrigo R, Barja P, Bosco C, Rencoret G, Sepúlveda-Martínez A, et al. Prediction of early and late pre-eclampsia from maternal characteristics, uterine artery Doppler and markers of vasculogenesis during the first trimester of pregnancy. *Ultrasound ObstetGynecol.* 2013;41:538–544. doi: 10.1002/uog.12264.
21. Kho EM, McCowan LM, North RA, Roberts CT, Chan E, Black MA, et al; SCOPE Consortium. Duration of sexual relationship and its effect on preeclampsia and small for gestational age perinatal outcome. *J Reprod Immunol.* 2009;82:66–73. doi: 10.1016/j.jri.2009.04.011.
22. Verwoerd GR, Hall DR, Grové D, Maritz JS, Odendaal HJ. Primipaternity and duration of exposure to sperm antigens as risk factors for pre-eclampsia. *Int J Gynaecol Obstet.* 2002;78:121–126.
23. Saftlas AF, Levine RJ, Klebanoff MA, Martz KL, Ewell MG, Morris CD, et al. Abortion, changed paternity, and risk of preeclampsia in nulliparous women. *Am J Epidemiol.* 2003;157:1108–1114.
24. Skjaerven R, Wilcox AJ, Lie RT. The interval between pregnancies and the risk of preeclampsia. *N Engl J Med.* 2002;346:33–38.
25. Lykke JA, Bare LA, Olsen J, Lagier R, Arellano AR, Tong C, et al. Thrombophilias and adverse pregnancy outcomes: results from the Danish National Birth Cohort. *J ThrombHaemost.* 2012;10:1320–1325. doi: 10.1111/j.1538-7836.2012.04773.x.
26. Al-Rubaie Z, Askie LM, Ray JG, Hudson HM, Lord SJ. The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review. *BJOG.* 2016;123:1441–1452. doi: 10.1111/1471-0528.14029.
27. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther.* 2012;31(1):42-8. doi: 10.1159/000335366. Epub 2012 Jan 13. PMID: 22248988.
28. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M, et al. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol.* 2017;49:756–760. doi:10.1002/uog.17455.
29. Choorakuttil RM, Patel H, Bavaharan R, Devarajan P, Kanhirat S, Shenoy RS, et al. Samrakshan: An Indian Radiological and Imaging Association program to reduce perinatal mortality in India. *Indian J Radiol Imaging.* 2019 Oct-Dec;29(4):412-417. doi: 10.4103/ijri.IJRI\_386\_19.
30. Choorakuttil RM, Rajalingam B, Satarkar SR, Sharma LK, Gupta A, Baghel A, et al. Reducing Perinatal Mortality in India: Two-Years Results of the IRIA Fetal Radiology Samrakshan Program. *Indian J Radiol Imaging.* 2022 Apr 19;32(1):30-37. doi: 10.1055/s-0041-1741087.
31. Choorakuttil RM, Rajalingam B, Satarkar SR, Sharma LK, Gupta A, Baghel A, et al. Effectiveness of the First Trimester Samrakshan Protocol for the Identification of Pregnant Women at High Risk for Preterm Pre-eclampsia. *Indian J Radiol Imaging.* 2022 Dec 26;33(1):98-100. doi: 10.1055/s-0042-1759856.

32. ACOG. First-trimester risk assessment for early-onset preeclampsia. Committee opinion No. 638. *Obstet Gynecol* 2015; 126: e25–27.
33. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015; 213: 62.e1–10.
34. O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, Wright A, Accuracy of competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; 49: 751–755.
35. Tousty P, Czuba B, Borowski D, Fraszczyk-Tousty M, Dzidek S, Kwiatkowska E, et al. Effectiveness of Different Algorithms and Cut-off Value in Preeclampsia First Trimester Screening. *J Pregnancy*. 2022 Apr 8;2022:6414857. doi: 10.1155/2022/6414857. PMID: 35433048; PMCID: PMC9012645.
36. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther* 2011; 29: 183–196.
37. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; 116: 402–414.
38. Roberge S, Nicolaides K, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2013; 41: 491–499.
39. Roberge S, Villa P, Nicolaides K, Giguère Y, Vainio M, Bakthi A, et al. Early administration of low dose aspirin for the prevention of preterm and term pre-eclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther* 2012; 31: 141–146