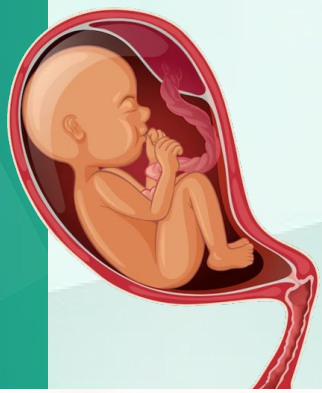
Society of Fetal Medicine
Kerala Chapter

FETOVERSE



SOCIETY OF
FETAL MEDICINE

A comprehensive Maternal-Fetal medicine update for clinical practice

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Theme

Preeclampsia screening in the first trimester: Deterrent action before the lightening strikes

Issue Editor- Dr. Seneesh KV

Scientific Contributors- Dr. Jyothi M, Dr. Meenu Batra, Dr. Seneesh KV, Dr. Vidyalekshmy R, Dr. Aryan Kashyap

Message from the Secretary

We take immense pleasure in introducing the first edition of FETOVERSE, the official newsletter of the Kerala chapter of the Society of Fetal medicine. This quarterly e-magazine is aimed at providing updates on various topics in maternal-fetal medicine of relevance for clinical Obstetric, fetal imaging and perinatal practice. It endeavors to encompass latest updates in the field of Maternal-fetal medicine from research conducted across various parts of the world and present in a lucid and comprehendible manner so that perinatal clinical and imaging practice can be refined and enhanced.

The first issue of FETOVERSE is being released on the occasion of the World Preeclampsia Day observed annually on May 22 as a healthcare awareness event in recognition of its immense perinatal impact. We sincerely hope the article would be of immense benefit to its readers.

Dr Seneesh Kumar V
Secretary, Kerala Chapter SFM

Message from the President

Pre-eclampsia, complicating 2-5 % of pregnancies (much higher in Asian and African countries), is an obstetrical syndrome associated with potentially deleterious sequelae for the mother, fetus and the neonate. Hypertensive disorders including pre-eclampsia is now the third leading cause for maternal mortality and second leading cause in certain confidential enquires especially from Kerala. Women who develop preeclampsia have on an average 10 years reduced from their lifespan.

This newsletter provides a comprehensive summary of the first trimester screening strategy for preeclampsia for the easy understanding of the perinatal health providers. It is anticipated that the screening strategy would soon be offered universally to all antenatal women in the first trimester in an effort to prevent the occurrence of this menacing disease.

Dr Jyothi Mancheri
President, Kerala Chapter SFM

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1. Background and pathophysiological basis for pre-eclampsia screening

Screening for maternal-fetal disorders in the late first trimester between 11-13^{+6} weeks has gained pre-eminence in view of its beneficial impact in the early prediction and subsequent prevention of adverse pregnancy outcomes [1]. These screening strategies conventionally fringe on a multimodality approach, encompassing quantification of certain biophysical and biochemical parameters along with a multivariate analysis of relevant aspects from maternal history [2].

Pre-eclampsia, recognizable in 2-5% of pregnancies has recently established itself at the forefront of the screening paradigms in view of the scope for early detection, availability of an effective intervention and the consequent circumvention of associated perinatal complications [3].

The objective of this article is to provide an insight into the first trimester screening for pre-eclampsia in light of the recent research followed by an overview of the prophylactic role of aspirin in its prevention.

Shortcomings in the risk factor based screening strategies

The prevailing strategies for pre-eclampsia screening were exclusively based on the identification of risk factors from maternal history during booking scan, and instituting aspirin, often at ill-defined doses, in the high risk women defined by the mere presence of one or more such factors **(table 1)** [4-8]. The suboptimal performance of these screening approaches is intelligible by their exclusive dependence on the presence of risk factors which are only present in 30% women. Lack of a proper algorithmic approach and ignoring the parameters which reflect the actual pathophysiological development of pre-eclampsia affect the performance of these strategies [9].

Table 1 An overview of the guidelines recommended by the professional societies for the screening of pre-eclampsia and administration of aspirin

US Preventive Services task force[*] [4]	NICE Clinical guidelines [#] [5]	SOGC Canada[**] [6]	ACOG[##] [7]	WHO[$] [8]
1+ Major criteria	**1+ Major criteria**	**High risk factors (one)**	**Any of the following**	**Any of the following**
▪ Renal disease	▪ Renal disease	▪ Previous PE ▪ Antiphospholipid syndrome ▪ Preexisting medical condition	Prior history of PE necessitating delivery before 34 weeks	▪ Previous PE ▪ Diabetes ▪ Chronic hypertension ▪ Renal disease ▪ Autoimmune disease ▪ Multiple pregnancy
▪ Autoimmune disease ▪ Diabetes Mellitus ▪ Chronic hypertension	▪ Autoimmune disease ▪ Diabetes Mellitus ▪ Chronic hypertension	▪ Maternal age > 40 years ▪ Obesity BMI > 35 kg/m^2 ▪ First ongoing pregnancy ▪ Interpregnancy interval > 10 years ▪ Booking systolic blood pressure > 130 mm hg or Diastolic blood pressure > 80 mm hg ▪ Multiple pregnancy	History of PE in two or more prior pregnancies	
▪ Previous PE ▪ Multiple gestation	▪ Previous PE			
2+ Minor criteria	**2+ Minor criteria**	**Moderate risk factors (> one)**		
▪ Primiparity ▪ Personal history factors	▪ Primiparity ▪ Multiple gestation	▪ Ethnicity-Nordic, Black, South Asian or Pacific Island		

▪ Maternal age > 35 years ▪ African American race ▪ Family history of PE ▪ BMI > 30 kg/m2	▪ Interpregnancy interval > 10 years ▪ Maternal age > 40 years ▪ Family history of PE ▪ BMI > 30 kg/m2	▪ Lower socioeconomic status ▪ Non-smoking ▪ Heritable thrombophilia ▪ Increased prepregnancy triglycerides ▪ Family h/o early cardiovascular disease ▪ Cocaine and methamphetamine use ▪ Inter-pregnancy interval of less than 2 years ▪ Reproductive technologies ▪ New partner ▪ Gestational trophoblastic disease ▪ Excessive weight gain in pregnancy ▪ Infection during pregnancy
Detection rate 90% (Early PE) 89% (Late PE) **False positive rate** 64.3%	**Detection rate** 39% (Early PE) 34% (Late PE) **False positive rate** 10.3%	

*** Aspirin to be started at a dose of 81 mg/day, if one major or two minor risk factors are present**
 # Aspirin to be started at a dose of 75 mg/day, if one major or two minor risk factors are present
**** 75-100 mg for the high-risk women daily at bedtime**
If any of the prior history is present, to start aspirin 60-80 mg in the late first trimester
$ 75 mg for the high-risk women to be started at the earliest

Pitfalls with existing societal guidelines

- **Risk factors for pre-eclampsia, which formed the basis of these guidelines, are present in a mere 30 % women.**
- **Some societal guidelines initially considered only multiparous women.**
- **Does not provide an exact risk for pre-eclampsia and merely considers presence or absence of certain risk factors without their multivariate analysis.**
- **These guidelines had unacceptable lower sensitivity and/or high false positive rates.**
- **Does not include biochemical and biophysical markers of poor placentation.**
- **The dosage of aspirin recommended by these guidelines varied leading to ambiguity in clinical practice.**
- **No large-scale research data or validation studies supporting these guidelines.**

Pathophysiological basis for preeclampsia screening

Pre-eclampsia is a clinico-pathological syndrome stemming from impaired placentation [3]. Normal placental implantation ensues trophoblastic invasion of the myometrial spiral arterioles in a two-stage process starting at 6-8 weeks of gestation and culminating at 16-20 weeks. During this process the spiral arterioles are remodelled to wide non-muscular channels insensitive to vasomotor control [10]. In impaired placentation on the other hand, an initial stage of deranged vascular remodeling of the spiral arteries abets suboptimal perfusion in the uteroplacental bed leading to a second stage of ischemia mediated sustained oxidative stress and systemic inflammatory response [11]. Endothelin-1 mediated final pathway is critical to clinical manifestations [**Figure 1**] [12]. Profound adaptations in the maternal cardiovascular hemodynamics accompany the molecular and histopathological placental changes [13]. Recently, a dysregulation at the fms-like tyrosine kinase -

1 (FLT1) locus in the fetal genome has been observed to be a fundamental molecular defect in women developing pre-eclampsia, underscoring the role of genetic predisposition [14].

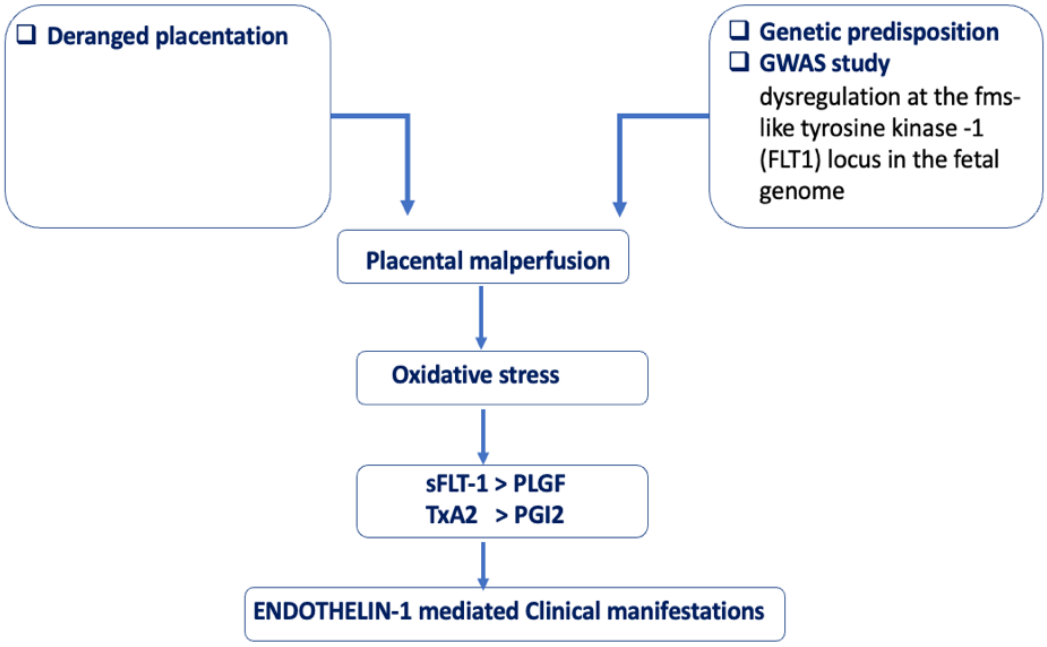

Figure 1 Schematic depiction of the current understanding of pathophysiological origin of pre-eclampsia.

Abbreviations: PGI2- Prostacyclin, PLGF- placental growth factor, TxA2- Thromboxane A 2

- **Pre-eclampsia occurs in genetically predisposed women with underlying impaired placentation.**
- **Hypoperfusion in placenta produces oxidative stress resulting in abnormal profile of cytokines and prostaglandins.**
- **These increase the serum levels of vasoconstrictors leading to hypertension.**

2. The Combined multimarker screening for pre-eclampsia

The combined multimarker screening for pre-eclampsia encompasses the documentation of maternal medical and demographic history, recording the mean arterial pressure (MAP), biochemical assay of the maternal serum placental growth factor (PlGF) and pregnancy-associated plasma protein A (PAPP-A), and measuring the mean Uterine artery (Ut A) pulsatility index (Ut PI) [15]. These biophysical and biochemical parameters reflect the adequacy of placentation.

The screening is performed at 11-13^{+6} weeks of gestation. The maternal risk factors are included in a multivariate algorithm which determines the *a-priori* risk (the background risk). The estimates of MAP, PlGF, PAPP-A and mean Ut A PI are converted to $\log_{10}$ transformed multiple of medians (MoM). Logarithmic transformation converts the aforementioned variables to Gaussian distribution while the use of MoM values eliminates the influence of various other variables such as gestational age, maternal height, weight or race. The *a-posteriori* risk (the final risk) for pre-eclampsia is estimated by the Bayes' theorem wherein the a-priori risk is modified by the estimates of the biophysical and biochemical parameters [15]. The Fetal medicine foundation (FMF), UK has proposed a competing risk model for the development of pre-eclampsia based on survival-time analysis [15]. This model firstly assumes that gestational age of delivery with pre-eclampsia is a continuous variable, and secondly, if the pregnancy was to continue indefinitely, all women would eventually develop pre-eclampsia. The development of pre-eclampsia before a specific gestational age depends on the competition between delivery before or after development of pre-eclampsia. In low risk pregnancies, the mean gestational age of development of pre-eclampsia as per the competing risk model is 54 weeks (standard deviation of 6.9 weeks). As women deliver much before this period, the incidence of pre-eclampsia is low in them. In the high-risk women, the gestational age of delivery with pre-eclampsia is shifted to left due to interplay of risk factors resulting in the development of pre-eclampsia before delivery [3,15].

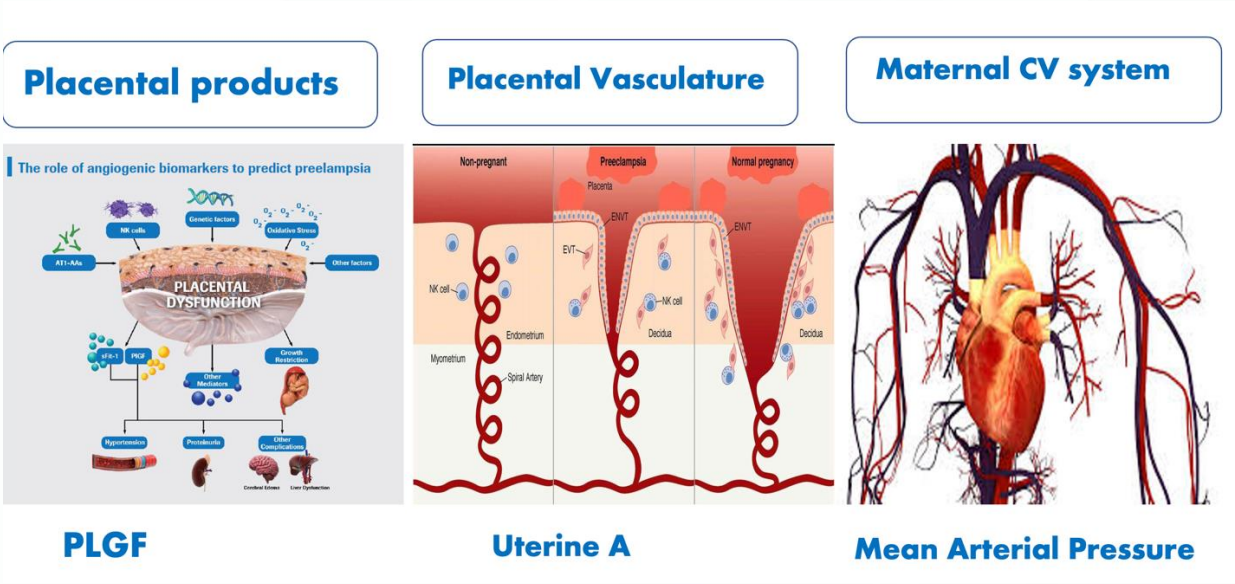

Figure 2 The parameters in combined screening for pre-eclampsia and their individual relevance in pathophysiological basis of the disease

Abbreviations: CV-cardiovascular, PLGF- placental growth factor, Uterine A-uterine artery

3. The individual components of the combined multimarker screening

a. Maternal demographic and medical history

Estimated detection rates (DRs) for pre-eclampsia requiring delivery before 34-, 37-, and 42-weeks' gestation in screening by multivariate analysis of maternal factors alone are about 36%, 33%, and 29% [false positive rate (FPR)- 5%], and 51%, 43%, and 40% (FPR-10%) [15].

Maternal characteristics, demographic factors and history to be documented in the first trimester pre-eclampsia (PE) screening protocol [14]

- Maternal age
- Maternal weight and Height
- Racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed)
- Past obstetric history: nulliparous, parous without prior PE, parous with prior pre-eclampsia
- Interpregnancy interval in years between the birth of the last child
- Gestational age at delivery (weeks) and birthweight of previous pregnancy beyond 24 weeks
- Method of conception: Spontaneous, ovulation induction, in vitro fertilization
- Cigarette smoking during pregnancy
- History of Chronic hypertension
- History of type 1 or 2 diabetes mellitus, insulin intake
- History of Systemic lupus erythematosus or Anti-phospholipid syndrome
- History of pre-eclampsia in the mother

*** Parity is defined as previous pregnancies(s) which crossed 24 weeks of gestation**

b. The Uterine artery Doppler

The Ut A insonation technique is illustrated in **Figure 3**. In the first trimester, spectral Doppler analysis of the ascending branch of the Uterine artery at the level of internal os is preferred over its apparent crossover of the iliac vessels, as it is more readily obtainable and reproducible at the former site [15]. The Ut A PI decreases with gestational age, increases with maternal weight and is higher in women of Afro-Caribbean origin [15]. The Ut A alone has a DR of 40-50% (FPR-5-10%) for early pre-eclampsia (requiring delivery < 34 weeks), while the addition of maternal medical history enhances the DR to 70-80% (FPR-10%).

A notch resulting from low velocities in the early diastole of the uterine artery waveform, objectively defined as 50 cm/s below the maximal velocity, reflects incomplete trophoblastic invasion. However, as a sole marker for predicting PE, Ut A notch is associated with a high FPR of 46-64% and a low positive predictive value [16]. The PI is a superior Doppler index as it is always measurable, even in the context of absent/reversed diastolic flow. The time averaged velocity (Tmax, denominator of PI) analyses all velocities in the sampled cardiac cycles, including the notch when present. Hence, PI is the preferred index for Ut A flow quantification. A PI value > 90th centile for the gestation is documented as resistant [17].

The Ut A PI values at the internal cervical os are higher than the iliac crossover site [l8], and are also higher when measured by the transvaginal route compared to the transabdominal route. Hence the appropriate nomograms should be used depending on the site and route of insonation [19]. In the absence of readily available nomograms in low resource settings, a Ut A PI of 2.35, which represents the 95th centile for 13th week, can be used a guide for Ut A flow adequacy.

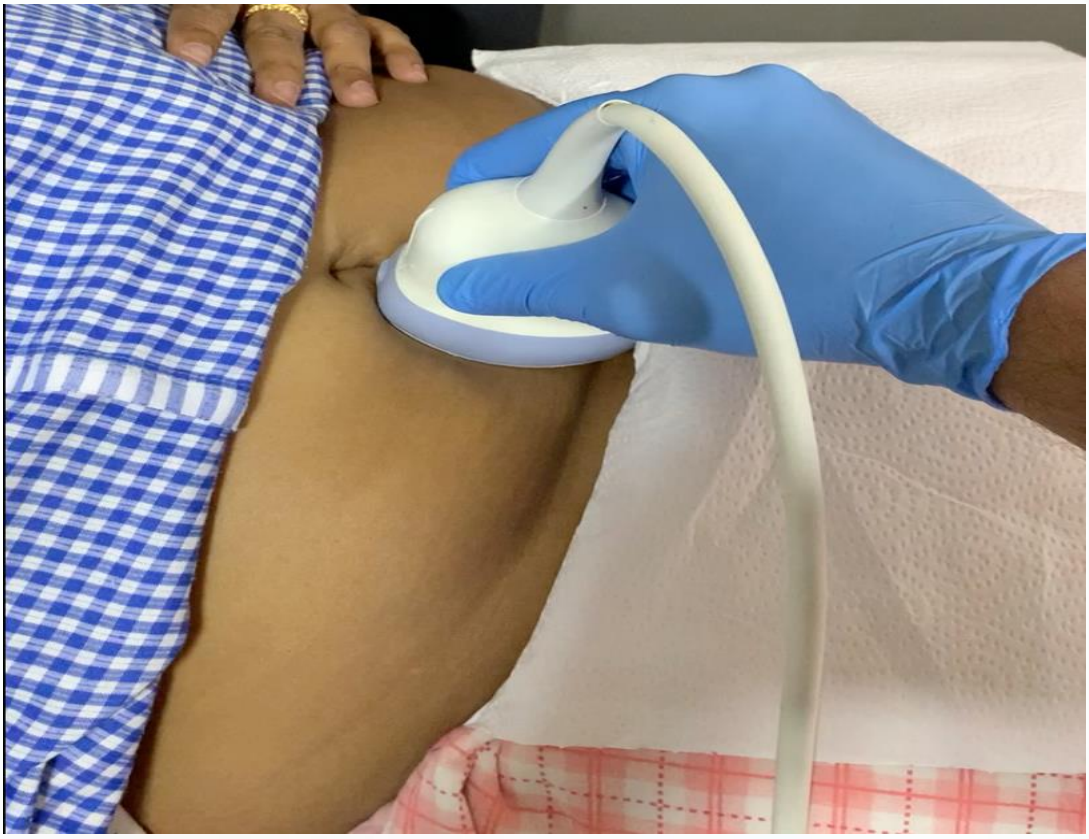

Figure 3 The placement of the transabdominal transducer for the performance of Uterine artery Doppler. The ultrasound examination is performed at 11- 13 $^{+6}$ weeks of gestation (in the same sitting as for the Nuchal translucency scan). Partially filled maternal bladder aids in the identification of the landmarks. The transducer is gently tilted to one side without lifting the transducer and the ascending branch of the Uterine artery of that side is identified with color Doppler. Same procedure is performed for the opposite side.

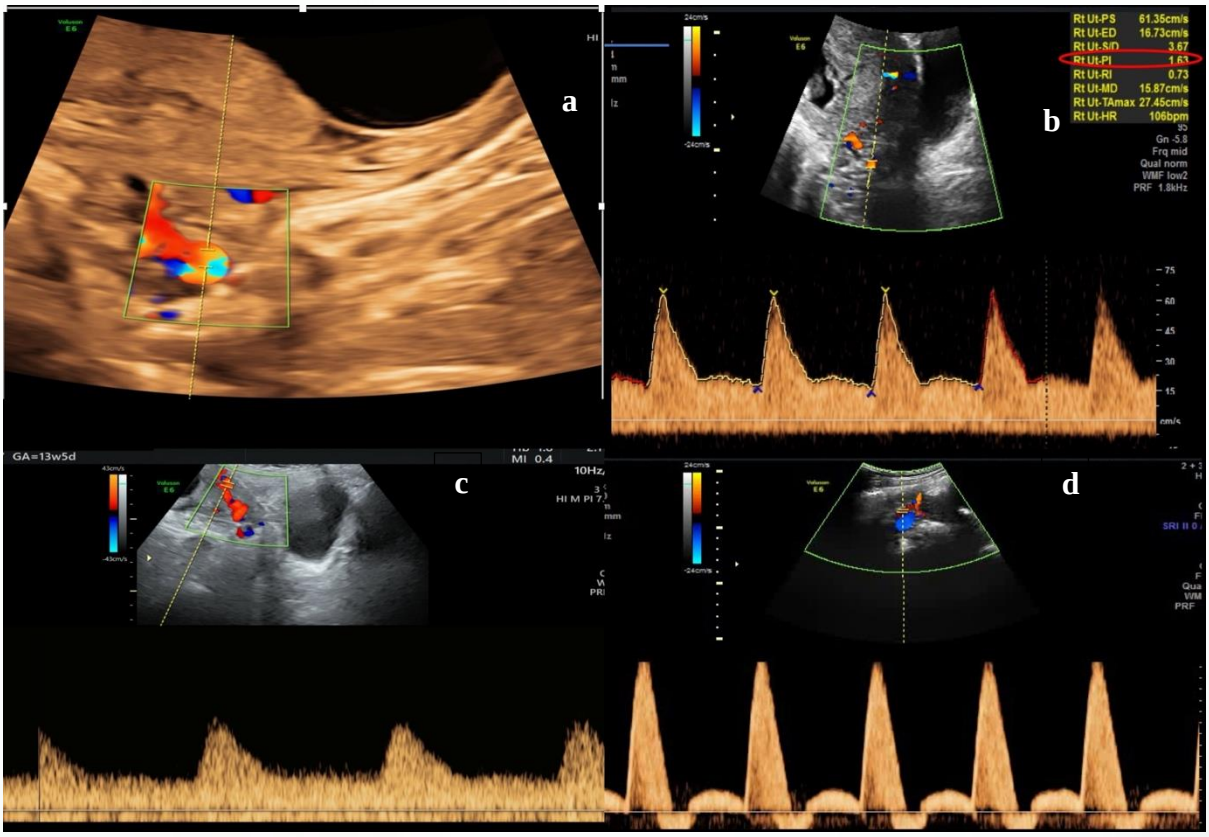

Figure 4 Color and spectral Doppler images showing-

(a) The Uterine artery insonated at the level of internal cervical os. It has a peak systolic velocity > 60 cm/s. Prominent aliasing (including paradoxical blue color) may be noted at low PRF settings due to the high velocity in the Uterine artery.

(b) Spectral Doppler is applied and three consecutive similar waveforms are obtained. The Pulse wave gate width should be 2 mm and the angle of insonation < 30 °. The pulsatility index of both sides are noted. The mean Uterine PI is calculated.

PI = Peak systolic velocity – End diastolic velocity/T max (time averaged velocity)

Mean Uterine PI = (Right Uterine A PI + Left uterine artery PI) ÷ 2

(c) Note the waveform of Arcuate artery which is distinct the Uterine artery. The vessel can be distinguished by a velocity of less than 60 cm/s, and its location away from the internal os.

(d) The waveform of maternal Iliac artery is markedly different.

- **The Uterine artery Doppler technique should be performed as per the criteria outlined by the Fetal Medicine foundation UK.**
- **The mean value of Uterine artery PI and its centile should be considered for risk assessment.**
- **The PI values and their centiles are available in ultrasound reporting softwares, the FMF website and app and the Fetal Medicine Barcelona website and app.**
- **The Uterine artery PI is affected by the gestational age, maternal weight, ethnicity of mother and route and site of insonation.**
- **Uterine artery notch and velocity does not carry greater significance than the PI value.**
- **A PI value of 2.36 is more than 95th centile for all gestational ages between 11-13^{+6} weeks.**
- **Uterine A Doppler alone has sensitivity of 50% (false positive rate of 10%) for early pre-eclampsia.**

c. The maternal serum biochemical markers

Several biomarkers have been investigated in the pathogenesis of pre-eclampsia [20]. Of these, PlGF has been most extensively studied and clinically validated. PlGF, a dimeric glycosylated glycoprotein produced by the cytotrophoblast, belongs to the VEGF (vascular endothelial growth factor) family and promotes non-branching angiogenesis leading to low resistance vascular network. Both VEGF and PlGF act by binding to transmembrane receptor FLT-1. The PAPP-A, also known as pappalysin, is a metalloproteinase produced by the syncytiotrophoblast that cleaves Insulin-like-growth factor (IGF) binding proteins 4 and 5, thus increasing the levels of IGF. This promotes mitosis and vasculogenesis. The individual performance of these analytes has been modest (DR- 60%, FPR- 10%) [21]. To ensure quality standards, the biochemical assay should be based on FMF, UK approved platforms (Delfia- Time resolved immunofluroassay, Roche and Kryptor- Chemi Luminescence Immunoassay).

- **The individual performance of biochemical factors in predicting pre-eclampsia is modest.**
- **Laboratories should use FMF UK approved platforms such as Delfia, ROCHE and KRYPTOR for assay of biochemical analytes and ASPRE algorithm for pre-eclampsia risk calculation.**
- **Maternal serum PAPP-A level of less than 0.4 MoM is a risk factor for development of fetal growth restriction. However, there is no evidence to recommend aspirin to prevent placental complications merely on this indication.**

d. Mean arterial pressure

Studies have shown that the MAP is superior method for documenting maternal blood pressure [22]. As per the FMF protocol for measuring MAP, the woman should be in sitting posture, relaxed with legs uncrossed and both arms at the level of heart **[FIGURE 5]** [23]. After a rest of 5 minutes, blood pressure is simultaneously recorded from both the arms using automatic calibrated sphygmomanometers. The procedure is repeated twice to obtain two sets of recordings. This method was found to be practically as effective as the methodology proposed by the National Heart Foundation of Australia, considered as the benchmark [22-23]. The addition of MAP improves the DR of the maternal apriori risk-based screening approach from 47% to 76% for early pre-eclampsia (FPR-10%).

Figure 5 showing the maternal position during the measurement of MAP. The woman should be relaxed and comfortably seated in a dedicated room. Two automatic calibrated sphygmomanometers should be tied to either arms and two sets of recordings should be obtained in an interval of 5 minutes.

e. Performance of the combined multimarker screening for pre-eclampsia

A study performed on 58 884 singleton pregnancies, showed that the above model detected 77% of preterm, 96% of early preterm (< 34 weeks), 38% of term (> 37 weeks) and 54% of all pre-eclampsia (FPR- 10 %) [15]. Secondary analysis from the ASPRE trial data, showed similar figures; DRs of 76.7% for preterm PE and 43.1% for term PE (FPR- 9.2% and risk cut-off of 1:100) [24].

- **The combined screening for pre-eclampsia provides risk for the development of preterm pre-eclampsia (pre-eclampsia developing prior to 37 weeks of gestation). However, occasionally the laboratory may also provide sub-risks for pre-eclampsia developing prior to 32 and 34 weeks of gestation.**
- **Screen positive result is when the FINAL RISK is greater than1:100.**
- **Screen positive woman should be seen by the Obstetrician as early as possible.**
- **Aspirin in optimum doses, optimised daily calcium intake and increase maternal-fetal surveillance should be instituted soon.**

4. The interventions after screen positivity

A risk ≥ 1:100 is usually reported as screen positive for preterm pre-eclampsia. Aspirin is the standard pharmacological intervention for prophylaxis in screen positive women [24], while increased maternal-fetal surveillance should replace normal prenatal care pathway.

(a) **Mechanism of action**-

Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug that acts primarily through its inhibition of the two cyclooxygenase isoenzymes (COX-1 and COX-2), involved in prostaglandin biosynthesis [25]. At lower dosages (60–150 mg/day) aspirin irreversibly acetylates COX-1, resulting in decreased platelet synthesis of TXA2 without affecting vascular wall production of PGI2. This is because the nucleated endothelial cells can rapidly replenish the COX enzyme unlike the nucleus deficient platelets. The inhibition of COX therefore lasts for the whole life of the platelet which is 7–10 days. The half-life of acetylsalicylic acid is short in humans (20 minutes), allowing the neo-synthesis of COX in the endothelium ensuring basal secretion of PGI2 25]. Aspirin also has a dose dependent reduction in the sFLT-1 levels mediated by COX-1 inhibition and anti-thrombotic action [26]. The net effect of these molecular changes is the prevention of deep placental lesions and preservation of spiral arteriolar transformation, increased production of PlGF, decrease in apoptosis and improvement of cytokine profile [27]. Ayala et al., observed that the effects of aspirin on ambulatory blood pressure were markedly dependent on administration time, with no effect compared with placebo when ingested upon awakening and statistically significant reduction when ingested 8 hours after awakening especially at bedtime ($p < .001$) [25].

(b) **The evidence**

The first randomized clinical trial on the impact of aspirin on pre-eclampsia prevention demonstrated a beneficial action when aspirin was initiated at a dose of 150 mg [28]. A

subsequently performed metanalysis of randomized trials on the use of low-dose aspirin in women at high-risk for pre-eclampsia demonstrated a risk reduction of 50% when aspirin was initiated at ≤ 16 weeks' gestation [relative risk (RR) 0.47, 95% confidence interval (CI) 0.36–0.62] [29].

The ASPRE (Aspirin for Evidence-Based Preeclampsia Prevention) trial was a multicenter, double blinded, placebo-controlled, randomized trial with intention-to-treat analysis and recruitment of 1776 singleton pregnancies found to be high risk in first trimester pre-eclampsia screening [30]. The primary outcome was comparison of preterm pre-eclampsia in the two groups (screen positive women given aspirin vs placebo treated). Screen positive women in the treatment arm were asked to take aspirin at a dose of 150 mg at bedtime. The study demonstrated a significant reduction of preterm pre-eclampsia [Odds ratio 0.38, 95% CI 0.20-0.74] and early preterm pre-eclampsia (< 34 weeks) [Odds ratio 0.62, 99% CI 0.34-1.14] in the aspirin treated group. A subsequently performed metanalysis concluded that aspirin reduced the risk of preterm pre-eclampsia when it was initiated at ≤16 weeks of gestation at a daily dose of ≥100 mg, with no impact on term pre-eclampsia [31].

(c) **Dosage and timing in pregnancy**

A dosage of < 300 mg per day is referred to as low dose aspirin. Screen positive women should have prophylaxis with aspirin at a dose of 150 mg taken at bedtime, to be initiated ≤ 16 weeks of gestation. The end points for the prophylaxis are completion of 36 weeks/delivery occurring < 36 weeks/women develops pre-eclampsia despite prophylaxis. Women weighing ≤ 40 kg can have the dose reduced to 100 mg [3].

The administration of low-dose aspirin at <11 weeks' gestation in women at high risk does not seem to decrease the risk of preeclampsia, gestational hypertension or fetal growth restriction [32]. Even though aspirin has no known teratogenic effects [33], it is prudent not to offer any drug prior to 8 weeks of gestation in the absence of robust safety data

and proven benefits. Aspirin started later than 16 weeks has shown no significant benefits in preventing pre-eclampsia which is explained by the shift in placental vascular development from proliferation to endothelial remodeling at mid-gestation for which aspirin has no beneficial action [34]. After 36 weeks, the larger dose of aspirin required at this period for beneficial effects may produce unnecessary neonatal effects. Aspirin has a much higher chance of development of resistance at lower doses (30%, 10% and 5% at doses of 81,121 and 162 mg respectively) [35].

(d) Clinical Impact of aspirin-

The beneficial impact of aspirin is greatest for early and preterm pre-eclampsia. This can be explained by the inverse relation of the prevalence of deep placental lesions with gestational age in women developing pre-eclampsia [36]. Additionally, the administration of low dose aspirin is associated with a 50% reduction in the incidence of fetal growth restriction, 60% reduction of preterm birth and 60% reduction in perinatal death [29].

(e) Adverse effects-

(vi.i.) Maternal-. A large population-based cohort study, involving 186 425 individuals being treated with low-dose aspirin and 186 425 matched controls without aspirin use, reported that aspirin use was significantly associated with an increased risk of major gastrointestinal or cerebral bleeding episodes (5.58 vs 3.60 per 1000 person-years) [37]. This risk, however, can be minimized by the restricted use of aspirin in screen positive women. Aspirin at a daily dose of ≥100 mg for prevention of preeclampsia that is initiated at ≤16 weeks of gestation, rather than >16 weeks, may decrease the risk of placental abruption or antepartum haemorrhage [38].

(vi.ii) Fetal

Third trimester use of aspirin in the routine dosage of 60-150 mg before 36 weeks is not associated with premature closure of ductus arteriosus or neonatal hemorrhagic complications [39].

(f) **Other interventions**

In women with low calcium intake (<800 mg/d), either calcium replacement (≤1 g elemental calcium/d) or calcium supplementation (1.5–2 g elemental calcium/d) may reduce the occurrence of both early- and late-onset PE. [3]. Women screen positive in pre-eclampsia screening need increased maternal-fetal surveillance. This includes blood pressure monitoring 1-2 times per week and serial fetal growth scans at 28, 32 and 36 weeks of gestation. Supplementation of Vitamin C, Vitamin E, antioxidants, dietary salt restriction and bed rest has not been proven to be useful [3]. The benefits of heparin have been inconsistent and available evidence do not merit clinical use [40].

- **Oral aspirin should be initiated before 16 weeks in pre-eclampsia screen positive women and continued till 36 weeks.**
- **A dosage of 150 mg should be offered, and the medicine should be taken at bedtime.**
- **A dosage of 100 mg should be offered for the occasional screen positive women with weight less than 40 kg.**
- **Dosages of 75 mg should be abandoned.**
- **There is no evidence of benefit in offering aspirin prior to 11 weeks and after 16 weeks of gestation.**
- **Aspirin should be stopped if the woman develops pre-eclampsia, the gestational age had reached 36 weeks or delivery is required due to other indications.**
- **There is no FDA category for Aspirin however there is no evidence for teratogenicity due to aspirin.**
- **Aspirin has no action on ductus arteriosus closure.**
- **It is not associated with increased risk of neonatal bleeding**
- **The absolute increase of maternal bleeding is marginal.**
- **There is no increased risk of abruption. Aspirin when started prior to 16 weeks in optimum dosage is actually associated with reduced risk of abruption.**
- **Minor vaginal bleeding during pregnancy is not an indication to stop aspirin.**
- **Aspirin postpones the development of pre-eclampsia in women to a later gestational age.**
- **Aspirin has secondary benefits of reduced incidence of small for gestational age fetuses and neonatal complication when used in optimised manner.**
- **Aspirin resistance can develop in 29% women when offered universally (without actual indications) and only in 5% when given in mothers who are screen positive.**
- **Aspirin therapy should be accompanied with enhanced daily calcium intake and periodic maternal-fetal surveillance.**
- **Besides pre-eclampsia screen positive women, the other indications for aspirin during pregnancy are antiphospholipid syndrome and women with thromboembolic conditions.**
- **The contraindications of aspirin are pre-existing maternal GI ulcers, aspirin hypersensitivity and h/o hematemesis.**

Screening in twin pregnancies

Chorionicity does not seem to be a significant determinant of the incidence of pre-eclampsia in twins. The estimated risk of preterm pre-eclampsia was 9.0% for dichorionic and 14.2% for monochorionic twins compared to 0.6% for singleton pregnancies [41].

The Ut A PI values in twin pregnancies are significantly lower compared to singleton pregnancies due to the larger placental implantation site in the former [42]. Similar to the singleton pregnancies, the MAP and Ut A PI values are increased while the serum levels of PlGF are reduced in twin pregnancies which eventually develop pre-eclampsia. However, in contrast to singleton pregnancies, the PAPP-A levels are raised in twin pregnancies destined to develop pre-eclampsia, the possible explanation being placental over-compensation [43].

The first trimester multimarker combined screening approach used for singleton pregnancies can be applied for twin pregnancies as well [3]. In a prospective screening study, at a cut off of 1:75, the DR of preterm pre-eclampsia and all pre-eclampsia for twin pregnancies were 99% and 97% (FPR-75%) [3,41].

A systematic review and metanalysis on the prophylactic use of aspirin in twin pregnancies observed that it was associated with a reduction in the incidence of pre-eclampsia and mild pre-eclampsia but not severe pre-eclampsia. The reduction of pre-eclampsia was not different between women randomized before (RR, 0.86: 95% CI, 0.41-1.81) or after (RR, 0.64: 95% CI, 0.43-0.96) 16 weeks of gestation. Hence additional studies are required before recommending low dose aspirin for all twin pregnancies [44].

5. Screening for Pre-eclampsia- overview

Pros

In strict parlance, pre-eclampsia is the only obstetrical condition that reasonably satisfies the criteria for screening in view of its potential detection in apparently healthy mothers in the preclinical stage and the availability of an effective and inexpensive intervention for screen positive cases. The screening algorithm has been prospectively validated in various countries [3]. A meta-analysis of individual patient data from the perinatal antiplatelet review of international studies (PARIS) collaborators, observed that the number needed to treat one case of pre-eclampsia with aspirin was 114, which was superior to other prenatal conditions [45]. The screening strategy performs best for preterm pre-eclampsia especially early pre-eclampsia which has the highest association with complications such as HELLP and eclampsia [3]. The International Federation of Obstetrics and Gynecology (FIGO) has benevolently endorsed the multimarker screening strategy for pre-eclampsia and has explicitly laid down its recommendations for the same **(Table 2)** [3].

Table 2 Executive summary of FIGO guidelines for the screening of preterm pre-eclampsia

The screening is universal. All pregnant women should be screened for preterm PE in the first trimester by a combined test which incorporates maternal risk factors and biomarkers as a one-step procedure.
The best combined test includes maternal risk factors, measurements of mean arterial pressure (MAP), serum placental growth factor (PlGF) and the mean uterine artery pulsatility index (Ut A PI).
When it is not possible to measure PlGF and/or Ut A PI, a baseline screening should comprise maternal risk factors and measurement of MAP.
A woman is considered high risk when the risk is ≥ 1:100 in the full combined test.
In low resource setting, a contingent approach for screening can be used wherein, first step comprises of maternal factors and MAP for all pregnancies followed by measurement of PlGF and Ut A PI in only the high-risk women.

Screen positive women should receive prophylaxis with low dose aspirin at a dose of 150 mg commenced at 11-13^{+6} weeks, to be taken at night until 36 weeks/till delivery/ PE is diagnosed.

Low dose aspirin should not be advised for all pregnancies.

In women with low calcium intake (<800 mg/day), either calcium replacement (≤1 g elemental calcium/day) or calcium supplementation (1.5–2 g elemental calcium/day) may reduce the burden of both early- and late-onset PE.

Cons

There is no discrete information on the cost effectiveness of pre-eclampsia screening with biochemical assay when it is not funded by a public health care system [3]. The FMF criteria for measuring the MAP is difficult to completely replicate in busy prenatal units. The suboptimal performance of screening for term pre-eclampsia and hence the need for a second screening in the third trimester needs introspection.

- **Combined screening for pre-eclampsia should be offered to all women between 11-13^{+6} weeks of gestation. Similar to Down syndrome screening, it should be an universal approach.**
- **Combined screening for early pre-eclampsia (< 34 weeks) has a sensitivity of 90% (risk cut-off 1:100, FPR 5%)**
- **Combined screening for preterm pre-eclampsia (< 37 weeks) has a sensitivity of 75% (risk cut-off 1:100, FPR 5%)**
- **Number needed to treat one case of Pre-eclampsia is 1:114.**
- **The prevention rate of pre-eclampsia in screen positive women with aspirin prophylaxis is about 82% for pre-eclampsia developing <34 weeks, and 62% in preterm pre-eclampsia.**
- **The additional benefits of aspirin are prevention of fetal growth restriction by 50%, premature birth by 60% and perinatal death by 60%.**
- **In low resource settings, a partial model with either or both Uterine artery Doppler and MAP can be offered.**
- **In India, most of the laboratories are offering biochemical screening for pre-eclampsia using the ASPRE algorithm.**

Among recent advances in pre-eclampsia screening is the use of maternal ophthalmic artery Doppler (OAD) which has shown potential value as a biomarker for pre-eclampsia screening, when used alone or in combination with established biomarkers (46-48). The OAD acts as a window to cerebral vasculature as it reflects the systemic inflammatory response that alters cerebral hemodynamics and plays a central role in the pathogenesis of pre-eclampsia.

The ophthalmic artery spectral doppler waveform has a characteristic biphasic waveform, that has two distinct peaks, namely S1 and S2, followed by a diastolic wave. The OAD to be characteristically dicrotic, meaning that the systolic peak is followed by a diastolic peak and low diastolic flow and a peak ratio, that is, the ratio of the diastolic peak to systolic peak, is useful in the screening of pre-eclampsia [49].

OAD- methodology during pregnancy

Identification of the ophthalmic artery on colour doppler and its optimized spectral waveform can be obtained as per the protocol described by Nicolaides et al (50).

The mother is placed in the supine position and asked to rest for 5 minutes. A 7.5-MHz linear transducer is then placed transversely and gently over her closed upper eyelid after application of conduction gel. A thin cling wrap film can be placed over the eyes to prevent soiling of the patient's eyes with gel. Colour flow Doppler is used to identify the ophthalmic artery, which is found superior and medially to the hypoechoic band representing the optic nerve.

Pulsed-wave Doppler is then used to record 3 to 5 similar waveforms. The angle of insonation should be kept at less than 20°, the sample gate is set at 2 mm to cover the whole vessel, the depth is 3.0 to 4.5 cm, the high-pass filter is 50 Hz, and the pulse repetition frequency is set at 125 kHz.

Minimal probe pressure should be used so as to reduce discomfort to the patient. Sometimes, due to rapid eye movements, tracing the ophthalmic artery in colour can become difficult. In such a scenario, the patient should be asked to close her eyes and look straight, which can be confirmed on 2-D ultrasound by identifying the position of the lens.

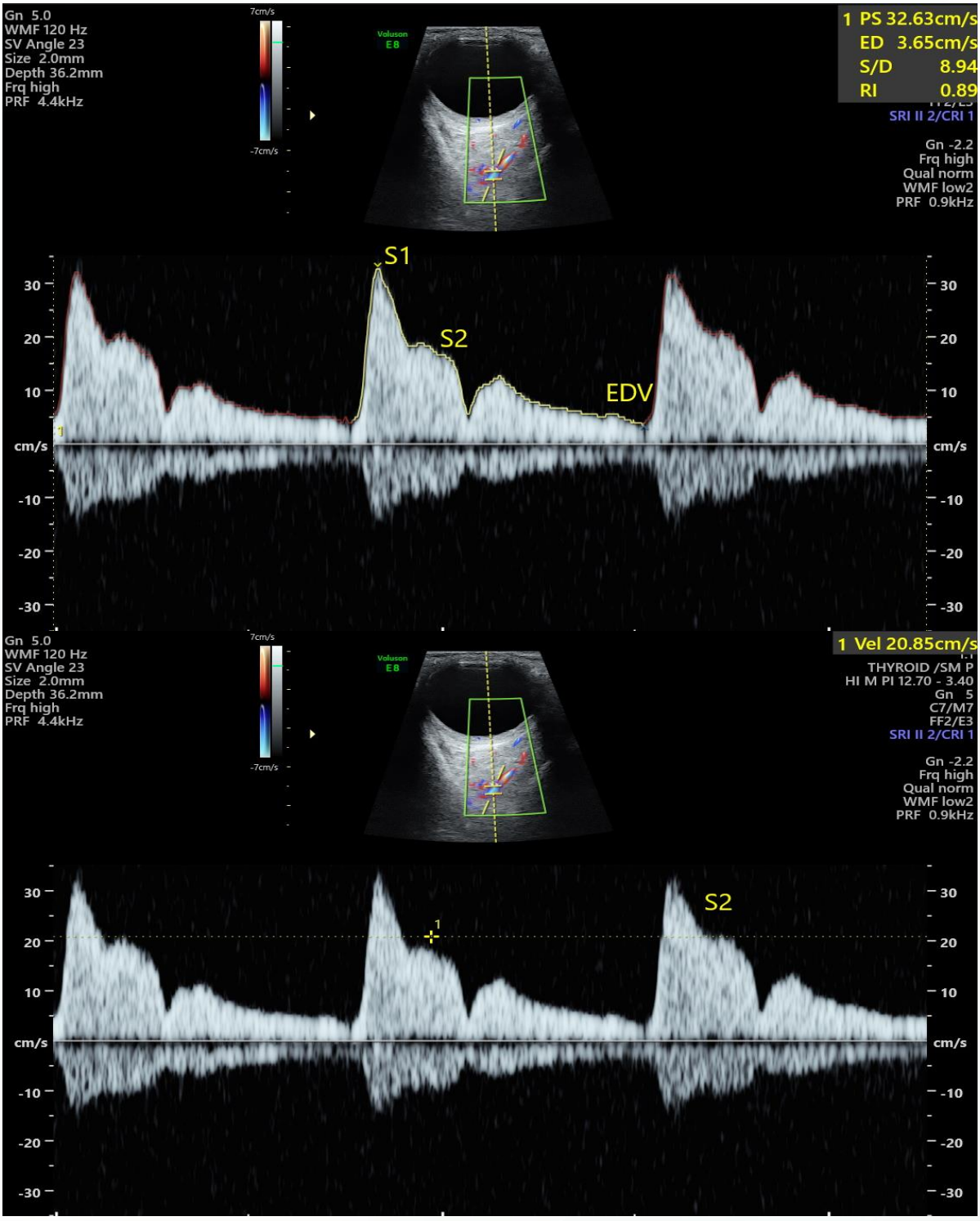

Figure 6 - Ultrasound images demonstrating the first and second peaks of systolic velocity and end diastolic velocity. The first systolic velocity is obtained using the auto method whereas the manual method has been used to measure the second peak systolic velocity.

The waveform from the ophthalmic artery is characterized by 2 peaks in systole. The following 4 indices have been studied for their diagnostic accuracy in pre-eclampsia: first peak systolic velocity (PSV), second PSV, pulsatility index (PI), and ratio of second to first PSV. The first PSV and PI are automatically obtained by the machine, the second PSV is measured manually, and the ratio of the second to first PSV is calculated (**FIGURE 6**). The best performance of screening for pre-eclampsia is achieved by taking the average of four measurements (two from each eye) however satisfactory results are also achieved by taking the average of one measurement from each eye [50].

OAD in pre-eclampsia: recent evidence

In recently published 3 prospective observational studies, unselected pregnancies were examined by OAD at $11\text{-}13^{+6}$ weeks, 19-23 weeks and 35-37 weeks respectively (8,9,16). Across all gestational ages, the PSV ratio (S2/S1 ratio) was found to be the most accurate parameter to be affected.

In the study done by Gana et al (46), out of 4066 unselected pregnancies that were screened, 114 pregnancies (2.8%) developed pre-eclampsia, including 25 (0.6%) that delivered with pre-eclampsia before 37 weeks of gestation. Their study showed that the PSV ratio was significantly increased in pre-eclampsia pregnancies, and the effect of pre-eclampsia depended on gestational age at delivery, with the deviation from normal being greater for early than for late pre-eclampsia. Addition of PSV ratio also improve detection rates for preterm pre-eclampsia when combined with traditionally used markers for pre-eclampsia screening.

Another study by Sapantzoglou et al (51), aimed to look at OAD indices in women between 19-23 weeks period of gestation. They also showed the PSV ratio to be significantly increased in pre-eclampsia, while other doppler indices were not predictive of pre-eclampsia. The PSV ratio improved the prediction of preterm pre-eclampsia provided by maternal factors alone (from 56.1% to 80.2%), maternal factors, MAP and UtA-PI (80.7% to 87.9%), maternal factors, MAP, UtA-PI and PlGF (85.5% to 90.3%) and maternal factors, MAP, UtA-PI, PlGF and sFlt-1 (84.9% to 89.8%), at a

FPR of 10%. Thus, OAD can be a valuable tool to improve detection rates for pre-eclampsia in low resource settings where the use of maternal serum biomarkers might not be feasible.

The study done by M.Sarno et al demonstrated that the ophthalmic artery PSV ratio at 35-37 weeks gestation can predict subsequent delivery with pre-eclampsia especially if this occurs within 3 weeks after assessment [**47].**

OPHTHALMIC ARTERY DOPPLER: WHAT THE FUTURE HOLDS?

OAD not only help us in understanding the cerebrovascular changes that occur in women with pre-eclampsia, but also open exciting avenues in PE detection and screening. The greatest advantage of OAD is in its ability to be used as a bedside, point of care test for PE detection, without the use of maternal serum biomarkers.

Future studies can be taken up in assessing OAD indices cut-offs that coincide with PE with severe features. These cut-offs can then be used to decide for pregnancy termination in low resource settings.

7. Current insights in clinical management of Preeclampsia

Preeclampsia is one of the leading causes of maternal and perinatal mortality worldwide **[52-53]**. It complicates 2–8% of pregnancies globally. It is a multisystem progressive disorder that can occur in pregnancy or postpartum. 10% of cases occur at less than 34 weeks (early preeclampsia). Pre-eclampsia (de novo) is gestational hypertension (SBP ≥ 140 or DBP ≥ 90 mm Hg) accompanied by one or more of the following new onset conditions at ≥20 weeks' gestation:

1. Proteinuria (PCR > 30 mg/mmol or ACR > 8 mg/mmol or urine albumin 2+ or more)

2. Maternal end-organ dysfunction, including:

- Neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headache, or persistent visual scotomata)
- Pulmonary oedema
- Haematological complications (platelet count < 150,000/μL, DIC, haemolysis)
- AKI (S Creatinine ≥ 1 mg/dL)
- Liver involvement (elevated transaminases > 40 IU/L) with or without right upper quadrant or epigastric abdominal pain

3. Uteroplacental dysfunction (abruption, FGR, abnormal umbilical artery Doppler, stillbirth)

Preeclampsia with severe features is defined as pre-eclampsia with severe hypertension that does not respond to treatment or is associated with ongoing or recurring severe headaches, visual scotomata, nausea or vomiting, epigastric pain, oliguria and severe hypertension, as well as progressive deterioration in laboratory blood tests such as rising creatinine or liver transaminases or falling platelet count, or failure of fetal growth or abnormal doppler findings.

Superimposed preeclampsia is defined as increase in hypertension or new onset or increasing proteinuria or worsening end organ function or uteroplacental dysfunction in a woman with chronic hypertension. Fetal growth restriction maybe a part of chronic hypertension per se & cannot be used as a diagnostic criteria for diagnosis of superimposed preeclampsia.

Pathogenesis of preeclampsia is complex and multifactorial. This includes abnormal placentation and defective spiral artery remodelling. Maternal immune maladaptation results in inflammation and imbalances in angiogenic and anti-angiogenic factors. This complex interplay results in preeclampsia.

Risk factors for preeclampsia include

Major risk factors	**Minor risk factors**
Chronic hypertension	Nulliparity
Type 1 or type 2 diabetes	Age > 40 years
Hypertensive disease during a previous pregnancy	Pregnancy interval > 10 years
Chronic kidney disease	BMI > 35
Autoimmune disease	Family h/o preeclampsia
	Multiple pregnancy
	ART

Symptoms of preeclampsia include severe headache, problems with vision such as blurring or flashing before the eyes, severe pain just below the ribs, vomiting, sudden swelling of the face, hands or feet.

Complications of preeclampsia

CNS	Eclampsia Cerebral haemorrhage Cerebral edema Stroke Cortical blindness Retinal edema
Renal	Renal tubular necrosis Renal cortical necrosis
Respiratory	Pulmonary edema Laryngeal edema
Hepatic	HELLP
Haematological	DIC , Haemolysis
Fetal	Abruption FGR Preterm delivery Stillbirth

Mainstay of management includes prediction and preventive strategies, timely detection, monitoring, treatment and delivery.

Preeclampsia prediction strategies include:

- Risk factors, maternal characteristics, HDP Gestosis score
- Biomarkers: such as PlGF, PAPPA, sFlt-1
- Ultrasound: uterine artery doppler, Ophthalmic artery Doppler

First trimester combined screening includes maternal characteristics, PlGF, PAPP-A, mean arterial pressure (MAP) and uterine artery Doppler, resulting in a detection rate of >90% for a

false positive rate of 5% for early pre-eclampsia.The sFlt-1/PlGF ratio can predict preeclampsia, with values less than 38 ruling it out for 1 week, 38-85 indicating high likelihood within 4 weeks, and more than 85 suggesting a likely diagnosis.

Preventive strategies include **[54-55]**:

- Low dose aspirin 150 mg/day at bedtime started preferably before 16 weeks has been shown to reduce early preeclampsia by 82% and late preeclampsia by 62%
- Calcium supplementation in women with low dietary intake
- Exercise unless no contraindications

There is no role for salt restriction, bedrest, nitric oxide donors, low molecular weight heparin, supplements such as magnesium, folate, Vitamin C and E, fish oil, garlic etc. Role of pravastatin and metformin remains investigational.

The key principles in managing diagnosed preeclampsia includes:

- **Control of hypertension:** Antihypertensives of choice include labetalol, methyldopa and nicardia. Severe hypertension should be emergently treated by IV Labetalol, IV Hydralazine or oral Nicardia to prevent stroke. Target BP is 135/85 mm Hg.
- **Monitoring** maternal and fetal wellbeing: Proteinuria testing only for diagnosis. PIH profile testing 2-3 times per week. Admit only if concerns present. CTG at diagnosis and as indicated. Ultrasound scans every 2 weeks or as indicated. In smaller centres, prediction models such as fullPIERS or PREP-S can be used to predict adverse outcomes and refer in time. A course of antenatal steroids if planning delivery before 34 weeks and MGSO4 for neuroprotection if <30 weeks.
- Optimising **delivery time:** The definitive treatment of preeclampsia is delivery to prevent complications from disease progression.

Timing of delivery

➢ >= 37 weeks	Initiate delivery
➢ < 37 weeks	➢ Surveillance and expectant management in cases without severe features ➢ Expeditious delivery if severe features present. Expectant management can be considered if less than 34 weeks with close surveillance

- **Mode of delivery** – Cesarean is performed for obstetric indications.
- **Intrapartum monitoring** — Continuous maternal and fetal monitoring
- **Fluids** — Avoid fluid overload as patients with preeclampsia are at risk for pulmonary edema and significant third-spacing. Fluid administration should be restricted to 80 mL/hour.
- **Seizure prophylaxis** -administer MgSo4 to all patients with impending eclampsia or uncontrolled severe hypertension to reduce the risk of developing eclampsia. MgSO4 also serves as treatment for eclampsia.

  Loading dose of 4g slow IV over 15 to 20 minutes followed by 1g/hr as a continuous infusion for 24hours from last seizure or delivery. Patients with renal impairment should receive a standard loading dose, but a reduced maintenance dose.
- **Postpartum:** Monitoring and antihypertensives. Thromboprophylaxis as indicated and ambulation. Contraception advice at discharge. Scheduled early review visits to taper drugs and follow up at 2 weeks, 6 weeks & 3-6 months to reassess. Counsel regarding recurrence risk and lifetime risk of adverse cardiovascular events. Long term adverse effects also include mental health disorders and adverse neurodevelopmental outcome if offsprings are exposed to preeclampsia in utero.

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