



The Samrakshan Screening Protocol for Pre-eclampsia in India

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Samrakshan is a national program of the Indian Radiological and Imaging Association (IRIA) that aims to reduce perinatal mortality in India with a primary focus on screening for the early identification of preterm pre-eclampsia (PE) and fetal growth restriction (FGR). These guidelines are intended for the use by fetal radiologists to encourage clinical practice based application, teaching and research in diagnostic imaging pertinent to preterm PE and FGR and as part of the Samrakshan program.

The aim of these Guidelines is to review the latest evidence to provide evidence-based recommendations regarding the role of ultrasound in screening and follow-up of PE. The primary focus of these guidelines are on the technical/clinical aspects of screening. The guidelines form a standard of clinical practice based on current evidence based guidelines in the global literature and evidence from the Samrakshan Screening Protocol based program implemented in India. These guidelines do not intend to establish a legal standard of care, as the evidence that underpins the development of these guidelines are dynamic and maybe influenced by individual circumstances, local protocol and available resources and changes in the evidence.

Pre-eclampsia: The Problem

The incidence of PE is estimated to vary between 8 and 10% among pregnant women in India compared to the global pooled incidence of 3% for PE. [1,2] PE is a significant clinical factor associated with preterm births (PTB), FGR, and perinatal mortality (PM) in India.

PE is multifactorial in its origin and affects several systems of the body. Defective placentation, oxidative stress, autoimmunity, platelet and thrombin activation, intravascular inflammation, endothelial dysfunction, an imbalance in angiogenesis and maternal cardiac maladaptation are some of the conditions that are associated with PE. Defective placentation is associated with early and severe PE and may not be associated with late onset PE. Risk factors, maternal vascular responsiveness, screening performance and the effectiveness of preventative measures also differ

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for early and late PE. Screening and preventative measures are more effective in preterm rather than term PE. [3-9]

Who are the intended users for the guidelines?

These guidelines are meant for the use of Radiologists in India with a basic degree or diploma in Radiology and an interest in Fetal Radiology and engaged in the assessment of Fetal Well-being. These guidelines are primarily meant for use in the care of pregnant women with singletons live fetuses who present to the Fetal Radiologist between 11-14 gestation weeks for fetal assessment. The population that accesses assessments at Fetal Radiology units are a mix of low and high risk cases.

Relevant Factors for Risk Assessment

The Samrakshan assessment of risk for preterm PE covers four broad areas. These include

1. Personal risk factors
2. Metabolic risk factors
3. Cardiovascular risk factors, and
4. Placental risk factors.

Primary modality of screening

The Samrakshan protocol utilizes ultrasound as the primary modality of screening. The primary evidence underpinning the use of USG for screening includes the ability to quantify incomplete transformation of spiral arteries by measuring impedance or resistance to the flow in uterine arteries using Doppler studies. Placental villous and vascular histopathological lesions are four-to-seven times more common in PE and are associated with increased resistance to uterine artery blood flow. [10,11]

Which Doppler Index is to be used?

The preferred Doppler Index for the examination of uterine artery resistance in the context of screening pregnant women for PE in Samrakshan India is the Pulsatility Index (PI). [12]

The systolic/diastolic ratio (SD ratio), resistance index and PI are the three common indices used in the assessment of uterine artery flow velocity wave forms. The Samrakshan Screening Protocol prefers the PI as it

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- Includes in its calculation the averaged value of all maximum velocities during the cardiac cycle,
- Is more stable and
- Does not approach infinity when there are absent or reversed diastolic values.

The Samrakshan protocol does not include assessment of bilateral uterine artery notching as

- Bilateral uterine artery notching is present in nearly 43% of normal 1st trimester pregnancies
- The assessment of notching has an element of subjectivity that can impact screening performance

The Samrakshan Protocol

Step 1

- Assign a unique ID for the woman.
- The unique ID will be used to document exams of the woman in all subsequent visits; Each woman will have only one unique ID
- The unique ID should preferably be alphanumeric, i.e, a mix of letters and numbers.
- The unique ID can include letters of the scan center, month, year and patient ID.
- The unique ID allotted for one woman will not be allotted for another woman.

Step 2

- Note the month of examination. It is preferable to write the month as text. Abbreviations are fine but maintain consistency in the way you document.
- Note the year of examination as YYYY
- Note the District the center of examination is located at
- Note the State the center of examination is located at.
- *Tip: maintain consistency in the way you enter these details. Use conventional modes with the first letter capitalized and subsequent letters in small caps. For example: Kerala. Longer state names can be shortened by the use of standard abbreviations. For example: UP, MP.*



Step 3

- Enter the Date of Birth of the woman as DD/MM/YYYY
- Enter the Date of examination as DD/MM/YYYY
- This information is important to estimate the age of the woman. A pragmatic reality in our country is that the Date of Birth may not be remembered by all pregnant women, especially those in the vulnerable sections. In such cases, try to estimate the age as accurately as possible including through the use of local historical events as a marker and then input the date of birth.

Step 4- Clinico-Demographic Details

- Enter the number of Fetus – Singleton Fetus.
 - The Form may be used to estimate the risk of preterm PE in twin pregnancies as well, in your clinical practice, and hence the form includes the type of twin MC/DC.
- Enter the height of the woman in centimetres
- Enter the weight of the woman in kilograms
- The height and weight should be documented. The body mass index will be derived from these variables.
- Enter Race as South Asian or Mixed (Since these are the demographics of primary interest)
 - Enter as South Asian if the woman is from the Indian subcontinent or has a lineage from the Indian subcontinent
 - Enter as mixed if the woman has an Indian subcontinent lineage mixed with other race lineages. Example: Indo-American, Indo-European, Indo-African, Indo-Japanese etc
- Enter Smoking as Yes or No. The definition of smoking will include inhalation of tobacco products, either regularly or infrequently.
- Enter if the pregnant woman's mother had a history of PE. Enter as Yes/No. If unsure, enter as No.
- Enter the type of conception as Spontaneous or Natural conception, Ovulation Induction or In Vitro Fertilisation



Step 5- Co-morbidity

- Enter the presence or absence of the following comorbidities
 - Chronic hypertension
 - Diabetes Mellitus
 - Systemic Lupus Erythematosus
 - Anti-phospholipid Syndrome
- These are the four main co morbidity of interest to determine the risk. The presence of other clinical morbidities should be elicited and documented as part of a complete clinical examination protocol

Step 6: Pregnancy Details

- Details of parity. Enter as Nulliparous or Parous. Nulliparous is defined as No previous pregnancy ≥ 24 gestation weeks
- Enter if the pregnant woman had PE in any past pregnancy as Yes or No. Enter as Not applicable if the woman is nulliparous.
- Enter Date of last delivery. If an exact Date is not available, try to estimate with reasonable accuracy based on recall of local historical events
- Enter GA at last delivery as week + days
- Enter interpregnancy interval as years

Step 7: Measurement of Mean Arterial Blood Pressure [13]

- Explain the procedure to the pregnant woman
- The blood pressure is measured with the pregnant woman in a seated position
 - Back should be straight and supported
 - Both Feet should be placed firmly and comfortably on the floor
 - The arms should be placed comfortably on a table, in front of the pregnant woman, at the level of the heart
- Measure blood pressure in both upper arms simultaneously
- Use a validated and calibrated digital blood pressure monitoring oscillometry instrument.
- Blood pressure monitoring oscillometry instruments are available online and at stores in almost all districts.



- *The use of a mercury sphygmomanometer is not recommended*
 - *We want to measure the blood pressure simultaneously in both upper arms*
 - *Simultaneous measurements are important to reduce potential differences in measures between the two arms compared to sequential measures.*
- Use an appropriately sized cuff
- Place the digital monitor facing away from the woman on the table
- Measure the blood pressure simultaneously in both arms
- Wait one minute.
- Again, Measure the blood pressure simultaneously in both arms
- *Don'ts:*
 - *It is recommended to do the measurement in a silent environment.*
 - *Do not use the opportunity to talk to the woman and engage in what may be considered relaxing small talk. They may impact on the measures.*
- Enter the systolic (2 readings) and diastolic (2 readings) measures
- The FMF online calculator will give the Mean Arterial Blood Pressure. Enter the Mean Arterial Blood Pressure.
- <https://fetalmedicine.org/research/assess/preeclampsia/first-trimester>

Step 8: Measurement of Fetal Crown Rump Length

- Enter the crown rump length. It is important to measure this accurately as it an important or the important parameter for dating. The range of acceptable CRL between 11 and 14 weeks of pregnancy is 45-84mms
- Do not subsequently change an assigned EDD.

Step 9: Measurement of mean Uterine artery PI [14]

- Transabdominal approach is the preferred mode as the risk algorithm utilized the transabdominal measurement values in the development of the algorithm. A transvaginal approach may be used only if a transabdominal approach is not feasible.



Measurement in the 1st Trimester

- Obtain the mid sagittal section of the Uterus and Cervix
- Tilt the transducer gently sideways while using colour flow mapping
- Identify uterine arteries with high velocity blood flow along the sides of uterus and Cervix
- Pulsed Wave Doppler Sampling Gate is narrow (set at approximately 2mm) and positioned on the uterine artery (ascending or descending branch) at the point closest to the internal cervical os.
- Insonation angle $<30^\circ$ and as close to 0 as possible.
- Peak systolic velocity should be $>60\text{cm/sec}$
- Measure PI when at least 3 identical wave forms are obtained
- Potential differences in Doppler Measures
 - Intra observer and inter observer variations
 - Uterine contractions
 - Changes in heart rate
- Adherence to standard protocol is important
 - Can measure Uterine PI in $>95\%$ of cases
 - Minimizes operator dependent variability
 - Reduces systematic errors in measurements
- **The 95th centile for mean uterine artery PI obtained using a transabdominal approach between 11 + 0 and 13 + 6 weeks is 2.35**
- *Uterine artery resistance is higher on transvaginal compared with transabdominal measurement; the 95th centile for mean uterine artery PI obtained using a transvaginal approach is approximately 3.10 for crown–rump lengths (CRL) up to 65 mm, gradually declining with increased CRL progressively declining thereafter to reach 2.36 at a CRL of 84 mm. The higher values with the TVS approach can be attributed to closer proximity of the transducer to the uterine artery and lower insonation angles.*
- The uterine artery PI may also be affected by maternal factors, including ethnic origin (PI is more in African races), BMI (decreasing PI with increasing BMI) and previous PE (associated with increased PI)



Measurement in the 2nd trimester

- The transabdominal measurement of the uterine artery PI in the 2nd trimester is similar to that in the 1st trimester.
- Transabdominal approach is preferred to transvaginal approach.
- **The 95th centile for mean uterine artery PI is 1.44 for the transabdominal approach and 1.58 for the transvaginal approach at 23 weeks**
- The 95th centile of the mean uterine artery PI decreases by about 15% between 20 and 24 weeks, and by <10% between 22 and 24 weeks.

Measurement in the 3rd trimester

- The transabdominal measurement of the uterine artery PI in the 2nd trimester is similar to that in the 1st trimester.
- **The 95th centile for mean uterine artery PI is 1.17 obtained using a transabdominal approach at 30–34 weeks**

Step 10: Enter Details in the Fetal Medicine Foundation online calculator

- Visit <https://fetalmedicine.org/research/assess/preeclampsia/first-trimester>
- Enter the details in the trimester specific online calculator
- Estimate Risk
- Samrakshan currently uses a 1 in 150 cut-off to identify pregnant woman as at high risk for preterm PE.
- This cut-off considers the high incidence of FGR in India and is aimed at offering the potential benefits of low dose aspirin to a larger population.
- This cut-off maybe revised based on accruing cumulative evidence.
- Samrakshan recommends preventative dosage of low dose aspirin, 150mg, once daily at bedtime, starting from 11-14 gestation weeks and to be continued till development of preterm PE, 37 gestation weeks, or childbirth, whichever is earlier. These recommendations are based on the ASPRE trial.



Levels of Evidence [14]

- Screening by first-trimester uterine artery PI $>$ 90th centile detects 48% of women who will develop early PE and 26% of those who will develop any PE, for a 10% screen-positive rate (EVIDENCE LEVEL: 2++).
- The 95th centile for mean uterine artery PI obtained using a transabdominal approach between 11 + 0 and 13 + 6 weeks is 2.35 (EVIDENCE LEVEL: 2+).
- Uterine artery resistance is higher on transvaginal compared with transabdominal measurement; the 95th centile for mean uterine artery PI obtained using a transvaginal approach is approximately 3.10 for crown-rump lengths (CRL) up to 65 mm, gradually declining with increased CRL thereafter (EVIDENCE LEVEL: 2+).
- The uterine artery PI may also be affected by maternal factors, including ethnic origin, BMI and previous PE (EVIDENCE LEVEL: 2++).
- As in the first trimester, uterine artery PI in the second trimester is higher when measured transvaginally (EVIDENCE LEVEL: 2++).
- The 95th centile for mean uterine artery PI is 1.44 for the transabdominal approach and 1.58 for the transvaginal approach at 23 weeks (EVIDENCE LEVEL: 2+).
- The 95th centile of the mean uterine artery PI decreases by about 15% between 20 and 24 weeks, and by $<$ 10% between 22 and 24 weeks (EVIDENCE LEVEL: 2++).
- Although uterine artery velocimetry can be assessed transvaginally, the most common method of uterine artery Doppler examination in the third trimester uses a transabdominal approach (EVIDENCE LEVEL: 4).
- The 95th centile for mean uterine artery PI is 1.17 obtained using a transabdominal approach at 30–34 weeks (EVIDENCE LEVEL: 2+).
- At a false-positive rate of 10%, maternal factors alone (including age, weight, ethnic origin, reproductive and medical history and smoking) could predict 49% of PE $<$ 37 weeks.



- The addition of PIGF increased this rate to 60%, and combined screening with maternal characteristics, mean uterine artery PI, mean arterial pressure and PIGF at 11–13 weeks predicted 75% of cases of PE < 37 weeks and 47% of cases of PE ≥ 37 weeks
- The algorithm, combining maternal factors, mean arterial pressure, mean uterine artery PI and PIGF, achieved a 100% detection rate for PE developing < 32 weeks, 75% detection for PE developing < 37 weeks and 43% detection for PE developing ≥ 37 weeks, for a 10% false-positive rate.
- A second-trimester model using uterine artery PI, maternal factors (including BMI, ethnic origin, previous obstetric history, smoking status, type of conception, medical history) and mean arterial blood pressure may detect as many as 100% of women who will develop early PE for a false-positive rate of 10%; the sensitivity for late PE and gestational hypertension is 56.4% and 54.1%, respectively.
- In the third trimester, a combination of maternal factors and sFlt-1 level may predict 83% and 38% of PE before and after 37 weeks, respectively, for a false-positive rate of 5%. The corresponding figures for a 10% false-positive rate are 94% and 51%, respectively.
- Prior screening in the first and/or second trimesters does not further improve prediction accuracy over that of third-trimester screening alone.
- Maternal and biochemical markers become more important for the prediction of PE in late pregnancy.

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