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REVIEW ARTICLE

Screening for Preeclampsia

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Abstract Pre-eclampsia, still continues to be a major cause of maternal and fetal morbidity and mortality, inspite of being an active area of research. The importance of early prediction of pre-eclampsia lies in the fact that it allows for timely initiation of preventive therapy. A combination of biophysical and biochemical markers are superior to other tests for early prediction of the development of pre-eclampsia. With the inversion of pyramid of antenatal care, preeclampsia screening in the first trimester needs to become the standard of care. Researchers now talk of predicting preeclampsia even in the third trimester to increase surveillance.

Keywords Pre-eclampsia · Early prediction · Maternal risk factors · Mean maternal arterial pressure · Ultrasound parameters · Biomarker · Pregnancy-associated plasma protein-A (PAPPA) · Placental growth factor

Screening for Preeclampsia

Preeclampsia is the most enigmatic disease which obstetricians have known for the longest duration of time and still like the Pandora's box a lot remains to be discovered. It is a major cause of maternal and perinatal morbidity and mortality [1] and the devious part is played by defective placentation. PE can be subdivided into early onset PE with delivery < 34 weeks' gestation and late onset PE with delivery ≥ 34 weeks. It is the early onset PE which is associated with great amount of neonatal morbidity in terms of prematurity [2]. Therefore with the shift in pyramid of antenatal care to first trimester it is logical that as far as screening for preeclampsia is concerned, it becomes imperative to identify early pregnancies at high risk of early onset PE and to undertake necessary measures to decrease the brunt of defective placentation and reduce the prevalence of the disease.

The screening tests for preeclampsia include tests which range from as simple as detailed history taking both obstetric and medical including maternal demographic characteristics, to a very doable test that is measurement of blood pressure of which MAP is validated, to a targeted ultrasound in the form of uterine artery pulsatility index (PI), and biochemical tests like plasma protein-A (PAPP-A) and placental growth factor (PlGF) at 11–13 weeks' gestation which can identify a large number of pregnancies at high-risk for early onset PE [3, 4].

Most importantly the need for screening for preeclampsia is important because there exists an evidence based strategy to prevent it. Low-dose aspirin for prophylactic use for prevention of preeclampsia has been investigated by a number of researchers. If the treatment is started at an early (< 16 week's) gestation there is a significant reduction in early-onset PE and this is supported by meta-analyses [5, 6] and taking this into consideration various national and international agencies currently recommend that women screened to be at high risk of PE should be offered aspirin therapy [7, 8]. "US preventive Services Task Forces Recommendation Statement" recently recommended of daily low-dose (81 mg/day) aspirin beginning in the late first trimester in high risk cases [9].

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This reinforces the need for early identification of high risk women with the objective of implementing targeted interventions for improving perinatal outcome.

Screening by Maternal History

Most of the professional bodies recommend that at the booking visit detailed history should be taken to ascertain her risk of preeclampsia and have issued guidelines for same (Table 1). However, screening strategies using maternal factors and history alone for detection of PE only perform moderately well at best. It has been demonstrated that maternal demographic characteristics, including medical and obstetric history are potentially useful in screening for PE only when the various factors are incorporated into a combined algorithm derived by multivariate analysis [10].

There is another risk model called competing risk model where it is assumed that all women would develop preeclampsia if the placenta malfunctions before delivery.

This approach, is based on a survival time model, which assumes that if the pregnancy was to continue indefinitely, all women would develop PE and whether they do so or not before a specified gestational age depends on a competition between delivery before or after development of PE [3].

Table 1 Maternal risk factors for preeclampsia

National Institute for Health and Care Excellence [7]
High-risk factors (one)
Hypertensive disease during a previous pregnancy
Chronic kidney disease
Autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
Type 1 or type 2 diabetes
Chronic hypertension
Moderate-risk factors (more than one)
First pregnancy
Age 40 years or older
Pregnancy interval of more than 10 years
BMI of 35 kg/m^2 or more at first visit
Family history of PE
Multiple pregnancy
World Health Organization [8]
Risk factors
Previous PE
Diabetes
Chronic hypertension
Renal disease
Autoimmune disease
Multiple pregnancy

Estimated DR of PE requiring delivery before 34, 37 and 42 week's gestation in screening by maternal factors are about 36, 33 and 29% respectively at FPR of 5%, and 51, 43 and 40% respectively at FPR of 10% [10]. Inspite of such low detection rates most of the professional bodies including American College of Obstetricians and Gynecologists recommends taking a detailed medical history only to assess a patient's risks for developing preeclampsia [11].

Screening by Maternal Biophysical Markers

Blood Pressure

Women who subsequently develop PE have higher systolic blood pressure and MAP before the onset of clinical disease. MAP is calculated by dividing the sum of the systolic and twice the diastolic blood pressure by three and is thus easily measurable.

The correct method of BP is that MAP should be measured by validated automated devices with women in sitting position with back supported and legs uncrossed that two measurements should be taken from each arm simultaneously with each arm supported at the level of the heart and that the average of the four measurements should be used [12].

Measurement of Blood pressure is very doable in every set up and if MAP is taken in first trimester along with maternal characteristics the detection rate of preeclampsia goes upto 74% for early preeclampsia, 63% for intermediate preeclampsia and 49% for late preeclampsia with a false positive rate of 10%. If we measure MAP in both first and second trimester we have a detection rate of 84% for early preeclampsia, 66% for intermediate and 53% for late preeclampsia with a false positive rate of 10% [13].

Uterine Artery Dopplers

The spiral arteries undergo a transformation to low resistance vessels by trophoblastic invasion and increases blood flow in the placental bed in pregnancy [15]. If this mechanism fails it leads to defective placentation [15, 16]. As predictors of preeclampsia average PI of both uterine arteries was taken at 22–24 weeks. It has a good negative predictive value which is better than positive predictive value and was considered better predictor for early onset severe PE however interventions have shown no statistically significant benefit at this stage to prevent preeclampsia and there was a definite need to get better as far as the screening performance of uterine artery for preeclampsia was concerned, so there came the need to measure uterine artery Doppler in first trimester as surrogate marker of defective placentation and this also supports the inversion of pyramid of antenatal care where emphasis

is shifting to first trimester screening. The uterine artery PI MoM is significantly increased at 11–13 week's gestation in women who subsequently develop PE.

Gestational age at screening, maternal weight, racial origin and history of pre-existing diabetes mellitus, affect the first-trimester uterine artery PI and therefore it should be it should be expressed as MoM after adjustment for these factors. The addition of uterine artery PI to maternal factors improves the DR from 36 to 59% and 33 to 40% at FPR of 5% and from 51 to 75% and 43 to 55% at FPR of 10% for PE requiring delivery before 34 and 37 week's gestation [4].

However even though detection rate of preeclampsia goes up with measurement of uterine artery Doppler, a reliable measurement of uterine artery PI is infact operator dependant. A sagittal section of the uterus should be obtained by using transabdominal ultrasonography and the cervical canal and internal cervical os needs to be identified. Color flow mapping is used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os. Pulsed wave Doppler is then used with the sampling gate set at 2 mm to cover the whole vessel and care should be taken to ensure that the angle of insolation is less than 30°. When three similar consecutive waveforms are obtained the PI is measured and the mean PI of the left and right arteries is calculated to ensure the accurate artery is not being sampled instead of the uterine artery [17]. It is important to ensure that the peak systolic velocity is greater than 60 cm/s.

Screening by Maternal Biochemical Markers

A plethora of biochemical markers have been investigated for the prediction of PE which includes PLGF, PAPP A, Inhibin-A and Activin-A, PP13, Disintegrin and Metalloprotease 12(ADAM12), Cystatin C, Pentraxin 3, P-Selectin, Fetal Hemoglobin. These markers are thought to be representative of reduced placental perfusion leading to placental ischemia-related damage with the release of inflammatory factors and abnormal oxidative stress [16, 18]. Maternal serum PAPP-A and PlGF are two biochemical markers that have stood the test of time and evidence as useful markers not only for aneuploidy screening but also for predicting preeclampsia [19]. Pregnancy-associated plasma protein-A is a syncytiotrophoblast—derived metalloproteinase, which enhances the mitogenic function of the insulin-like growth factors by cleaving the complex formed between such growth factors and their binding proteins [20]. PAPP-A plays an important role in placental growth and development, therefore low serum PAPP-A is associated with a higher incidence of PE. Placental growth factor is a glycosylated dimeric glycoprotein, which is a member of the vascular endothelial growth factor subfamily. PlGF is proangiogenic and has been speculated to play a role in normal pregnancy, and decrease in its level has been implicated in development of PE [21, 22]. These reduced levels of serum PlGF are evident from both the first- and second-trimesters of pregnancy [23, 24].

In biochemical testing, the serum metabolite concentration is then expressed in a multiple of the expected median (MoM) of the normal [25] because both PAPP-A and PlGF have shown to be affected by gestational age at screening, maternal weight, racial origin, cigarette smoking, conception by IVF, nulliparity and pre-existing diabetes mellitus. In addition, serum PlGF is also affected by maternal age [26]. The addition of maternal serum PAPP-A and PlGF to maternal factors improves the DR from 36 to 60% and 33 to 43%, at FPR of 5%, and from 51 to 74% and 43 to 56%, at FPR of 10%, for PE requiring delivery before 34 and 37 weeks' gestation [14].

Screening by Maternal Biochemical and Biophysical Markers

Effective screening for PE can also be achieved by a combination of maternal factors, biochemical and biophysical markers. If MOM values of biochemical markers serum PAPP-A and PlGF, MAP and uterine artery PI in pregnancies with PE, are added to the maternal characteristics all four markers together increase the risk assessment of preeclampsia. Estimated DR of PE requiring delivery before 34, 37 and 42 weeks' gestation in screening by maternal factors with biochemical and biophysical markers are 93, 61 and 38%, respectively, at FPR of 5%, and 96, 77 and 54%, respectively, at FPR of 10% [14]. Here comes the role of intervening by giving aspirin before 16 weeks to prevent preeclampsia [27–29].

Screening in Third Trimester

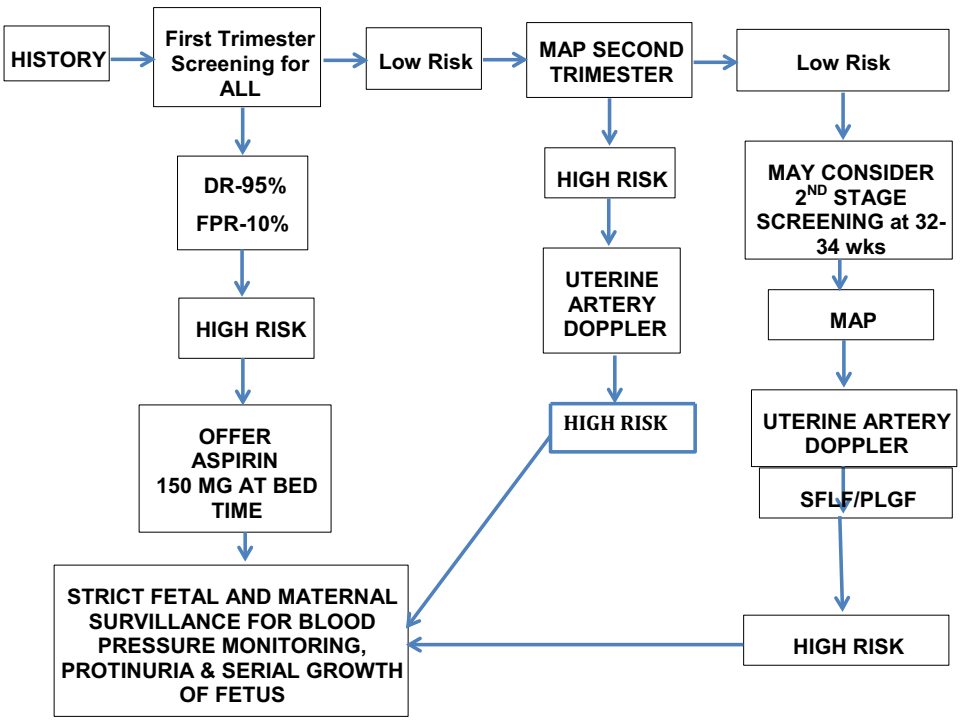
For early onset PE the first-trimester of pregnancy gives us an opportunity to do a good screening. However, late onset PE still remains a challenge. Nicolaides and his team therefore proposes screening at 11–13 weeks, which mainly aims at early onset PE prediction and here comes the role of aspirin in the dose of 150 mg at bed time which if started before 16 weeks substantially decreases the incidence of early onset preeclampsia [5, 36]. The second stage screening at 30–33 weeks, is required for predicting preeclampsia that aims at intensive close monitoring of these pregnancies by blood pressure measurements, proteinuria and intensive fetal monitoring for growth restriction and warrants delivery at or after 34 weeks [30]. This particular combines maternal characteristics and history, biochemical and biophysical markers at 30–33 week's gestation to estimate the risk of developing PE requiring delivery within selected intervals from the time of

screening. They have used MAP, UTPI, PLGF (pro angiogenic), and SFLT (antiangiogenic) at 30–34 week's gestation to examine the potential improvement in performance of screening by maternal factors along with the addition of each biomarker and combinations of biomarkers. In pregnancies that developed PE, the values of MAP, UTPI, and SFLT were increased and PLGF was decreased. For all biomarkers the deviation from normal was greater for preterm-PE than term-PE and therefore, the performance of screening was inversely related to the gestational age at which delivery become necessary for maternal and/or fetal indications. Combined screening by maternal factors, MAP, UTPI, PLGF, and SFLT predicted 98% of preterm-PE and 49% of term-PE, at a false-positive rate of 5% [31]. The main aim of third trimester screening is to identify the subgroup that will develop severe PE requiring delivery within the subsequent 1–4 weeks. In such high-risk pregnancies measurement of serum PlGF or soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF ratio are highly accurate in identifying the target group [32, 33]. In pregnancies complicated by PE, compared with normal pregnancies, serum PlGF MoM is decreased, and sFlt-1 MoM is increased. Researchers are now talking about screening as late as 35–37 weeks to predict preeclampsia [34].

Screening in Second Trimester

The main value of the 22 weeks assessment is to identify first the high-risk group for development of early PE that would then require close monitoring for development of high blood pressure and proteinuria at 24–32 weeks and second the high-risk group for preterm PE that would require reassessment at around 32 weeks and on the basis of such assessment stratification into a high-risk group in need of close monitoring at 32–36 weeks and a low-risk group that would be reassessed at 36 weeks. In pregnancies that developed PE the values of MAP, UTPI, and SFLT were increased and PLGF was decreased. For all biomarkers the deviation from normal was greater for early than for late PE and therefore the performance of screening was inversely related to the gestational age at which delivery became necessary for maternal and/or fetal indications. Screening by maternal factors predicted 52, 47, and 37% of PE at < 32, < 37, and 37 week's gestation respectively at a false-positive rate of 10%. The respective values for combined screening with maternal factors and MAP, UTPI, and PLGF were 99, 85, and 46%. The performance was not improved by the addition of SFLT. Therefore performance of screening for PE by maternal factors and biomarkers in the middle trimester is superior to taking a medical history [35]. Performance of screening for PE by this method is by far superior to those recommended by ACOG [11] or NICE [7] where screening performance of preeclampsia is very poor.

Algorithm We Can Follow for Preeclampsia Screening



Summary

1. We should follow universal screening for all pregnancies in the first trimester because it has a detection rate of 95% with a false positive rate of 10%. This method of screening is far superior to screening by history alone as recommended by ACOG and NICE.
2. This early screening gives a window of opportunity to offer aspirin which as per the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial has demonstrated that aspirin at 150 mg/day given at night to high-risk women at 11–13 weeks till 36 weeks reduces the risks of PE at < 32 and < 37 week's gestation by 80 and 60% respectively. There was no reduction in the risk of PE at > 37 week's gestation [36].
3. There is role of second stage screening for preeclampsia at 30–33 weeks for early detection of those who are likely to develop preeclampsia in the next 4 weeks, which would enable us to increase fetal and maternal surveillance.

Conclusion

Preeclampsia continues to remain the most dreaded obstetric complication of pregnancy. Effective first trimester screening at 11–13 weeks gestation in which biophysical and biochemical markers when combined with maternal characteristics for predicting early onset PE is now achievable with a DR of about 95% and a FPR of 10%. The motive remains to identify those cases that would potentially benefit from prophylactic pharmacological interventions to improve placentation. It is foreseen that a similar integrated screening at 30–33 weeks in future will emerge as a protocol for effective prediction of pregnancy complications that develop during the third-trimester. This would help to tailor make the monitoring and content of subsequent visits for selection of the best time for delivery. Prospective studies are underway to confirm the predictive abilities of the biomarkers identified both for early and late onset PE as well as for other related obstetric complications.

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