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ORIGINAL ARTICLE

First Trimester Screening for Pre-eclampsia and Fetal Growth Restriction

Lakshmy Ravi Selvaraj[1] · Nity Rose[1] · Meenakshi Ramachandran[1]

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Abstract This paper is an analysis of the effectiveness of various first trimester markers in detecting uteroplacental insufficiency. The various parameters used for screening in 3373 women were uterine artery pulsatility index (PI) >90th percentile, maternal characteristics, mean arterial pressure (MAP), PAPP-A lower than 0.5 MoM, and PlGF test. Adverse pregnancy outcomes related to uteroplacental insufficiency, namely low birth weight, fetal loss, delivery before 36 weeks (due to abnormal fetal Doppler or oligohydramnios), and hypertension were assessed. Adverse outcomes were found in 37 % of patients who had high uterine PI, in 52 % of cases that had a positive risk after inclusion of maternal characteristics, MAP, and uterine artery Doppler, 55 % of women with low PAPP-A values, 85 % in cases that had both low PAPP-A values and high uterine artery PI, in all the cases positive for early onset pre-eclampsia (PE), and in 65 % of cases positive for late onset PE after inclusion of all parameters mentioned above with PlGF testing. Hence, PlGF test had the maximum detection rate for early onset PE. However, the predictive efficacy for detection of PE and fetal growth restriction (FGR) is quite good when PAPP-A is combined along with first trimester risk prediction using maternal characteristics, MAP, and uterine artery PI. The adverse outcomes were very minimal in the screen negative group, thus first trimester screening for PE and FGR definitely helps in triaging patients earlier in pregnancy giving the advantage of adding low-dose aspirin and increasing surveillance in screen positive group which would help us in minimizing adverse perinatal outcomes.

Keywords First trimester screening · Pre-eclampsia · Fetal growth restriction · Uterine artery Doppler · PAPP-A · PlGF · Serum biochemistry · Mean arterial pressure

Introduction

Hypertensive disorders of pregnancy are one of the most common medical disorders encountered in pregnancy. Globally, pre-eclampsia (PE) is responsible for approximately 50,000 maternal deaths annually and is a leading cause of perinatal morbidity and mortality [1]. Many studies quote about 15–18 % of maternal mortality to be associated with PE [2–4]. One in six babies born to pre-eclamptic mother is often preterm or severely growth restricted [5]. Neonatal morbidity and mortality is approximately 7–9 % in pregnancies complicated with PE [6, 7].

With the current standards of prenatal care we have not devised an effective method to identify relatively common obstetric problem like PE in low-risk populations [8] and we are still uncertain about the best screening and monitoring strategies [9]. The performance of screening can be improved by combining history with a series of biophysical and biochemical markers which are altered early in the first trimester of pregnancy in cases that subsequently develop PE [10, 11]. Recent studies have established the benefits of the use of low-dose aspirin early in gestation in the high-risk population to reduce the incidence of PE and fetal growth restriction (FGR) [12]. The aim of this study is to analyze the effectiveness of various first trimester screening markers in identifying uteroplacental insufficiency.

✉ Lakshmy Ravi Selvaraj
drlakshmiravi@gmail.com

[1] Shri Lakshmi Scan Centre, 185/386-A, Govindhachetty Street, N.C.R. Complex, Kaveripattinam, Krishnagiri, Tamil Nadu 635112, India

Material and Method

All women who were referred to us for first trimester 11–14 weeks scan from June 2012 to June 2015 were included in the study. Fetuses with structural malformations and proven aneuploidy were excluded. Screening for PE was done for 3373 cases after obtaining informed consent from them. Biophysical or biochemical tests or combined testing were done in this group as per the request of the referring clinicians. The parameters used for screening in this study were uterine artery Doppler, risk prediction of PE and FGR by FMF (Fetal Medicine Foundation) Astraia software after incorporating maternal characteristics, mean arterial pressure (MAP), and uterine artery pulsatility index (PI), pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PlGF). Seventy-two cases were lost to follow-up and hence excluded from the study.

Uterine artery PI measurements were recorded as per the FMF guidelines by doctors who had obtained the FMF certificate of competence in screening for PE. Unilateral or bilateral uterine artery PI >90th percentile was considered as screen positive. Blood pressure measurement was taken by an automated device in this study after a rest of 5 min in both the hands. Mean arterial pressure, maternal characteristics, and uterine artery PI were included and the risk for PE and FGR was calculated as per the FMF Astraia software.

In patients who were referred for serum biochemistry as a part of aneuploidy screening, PAPP-A values <0.5 MoM (multiples of median) were taken as a screen positive parameter in our study. The patients referred for PE screening with PlGF were also included in the study group.

Adverse pregnancy outcomes related to uteroplacental insufficiency were assessed. Details of these patients were obtained from the respective clinicians and were followed till delivery to analyze the perinatal outcome. As PE and FGR are considered as a disease spectrum related to uteroplacental insufficiency, the outcome parameters chosen for the study were low birth weight (birth weight <2.5 kg at term or <10th percentile for that gestational age), delivery before 36 weeks due to abnormal fetal Doppler or oligamnios, fetal loss, and maternal hypertension.

To analyze the effectiveness of each screening parameter, the study cohort was categorized into five groups. Group I included patients with unilateral or bilateral uterine artery; PI >90th percentile. Group II included patients who were predicted to have high risk after inclusion of maternal characteristics, MAP and uterine artery PI. Patients with PAPP-A value <0.5 MoM were classified under Group III. The subset of patients in Group III who also had high risk after inclusion of maternal characteristics, MAP, and uterine artery PI came under Group IV. Group V included patients who were screen positive after PlGF testing.

Results

Out of the 3301 patients, 265 were found screen positive with high uterine artery PI. Adverse outcomes were seen in 37 % of these cases. After inclusion of maternal characteristics, MAP with uterine artery PI, and the risk for PE and FGR predicted, 596 patients were screen positive. Adverse outcomes were seen in 52 % of these cases.

Of 1147 patients who opted for serum biochemistry, 112 patients had a low PAPP-A of less than 0.5 MoM. Thirty six cases with low PAPP-A values were also screen positive in Group II and were categorized as Group IV. Adverse pregnancy outcomes were seen in 55 % of cases in Group III and 85 % of cases in Group IV, respectively.

Of 400 patients who underwent combined PlGF testing, 52 were screen positive, 23 were positive for early onset PE, and 29 for late onset PE. All cases in the early onset group had one or more adverse outcomes. However, only 75 % in late onset group had adverse outcomes. The study results are illustrated in Table 1.

Outcomes were also taken in the screen negative cases in Group IV and Group V as illustrated in Table 2. Of screen negative patients in Group V, 39 % had adverse outcomes making PlGF test less specific. In Group IV, 729 patients neither had high uterine artery PI nor had low PAPP-A values, and were screen negative after inclusion of maternal characteristics and MAP. In this group of cases, only 11 % had adverse outcomes and the fetal loss was 0.5 %.

Discussion

The National Institute of Clinical Excellence (NICE) recommends a screening strategy by which women with age greater than 40 years, body mass index $\geq$30 kg/m^2, pre-existing vascular or renal disease, nulliparity or pregnancy interval of >10 years, prior or family history of PE, and multiple pregnancy have an increased probability of developing PE. But unfortunately this categorizes more than 60 % of pregnant women as high-risk and predicts <30 % of those destined to develop PE [13–16], hence screening for PE using maternal history alone is very unreliable. Poon et al. [17] and Akolekar et al. [18] in their study had emphasized the importance of combined

Table 1 Illustration of adverse outcomes in the screen positive cases of various groups studied

Adverse outcomes	Group I	Group II	Group III	Group IV	Group V	
	Uterine artery PI (%)	Uterine art. PI, MAP, and maternal characteristics (%)	Low PAPP-A (%)	Uterine art. PI, MAP, and maternal characteristics & PAPP-A (%)	PlGF (%)	
					Early	Late
Low birth weight	19.5	25	39	42	33	30
BP	8	15	18	23	65	55
IUD	3	3.1	3.4	15	14	5
Delivery before 36 weeks	10	14	12	8	28	20
Normal outcome	63	48	45	15	0	35

BP blood pressure, *IUD* intrauterine death, *MAP* mean arterial pressure, *PAPP-A* pregnancy associated plasma protein-A, *PlGF* plasma placental growth factor, *PI* pulsatility index

Table 2 Illustration of adverse outcomes in the screen negative cases in group IV and group V

Adverse outcomes	Screen negative (%)	
	Group IV	Group V
Low birth weight	4	14.9
BP	3.9	14
IUD	0.5	1.3
Delivery before 36 weeks	2.1	11.7
Normal out come	89	61

BP blood pressure, *IUD* intrauterine death

inclusion of maternal characteristics, biophysical and biochemical testing at 11–13 weeks gestation to improve predictive efficacy in the screening for PE.

Pre-eclampsia is classified clinically as early onset PE which is diagnosed and requires delivery before 34 weeks and late onset PE. Though the incidence of early onset PE is less (0.4–1 %), it amounts to a significant burden of disease as it is associated with prematurity, FGR, and long-term perinatal, and maternal morbidity [19–22]. The pathogenesis of early onset PE or "placental PE" is attributed to impaired trophoblastic invasion of spiral arteries resulting in placental ischemia and oxidative stress [20, 21, 23, 24]. This high-resistance blood flow in uteroplacental circulation can be measured noninvasively by uterine artery Doppler ultrasonography [17].

Late onset PE or "maternal PE" is thought to be a secondary maternal response to endothelial dysfunction. Placenta may be normal or with minimal impairment as evidenced by histopathology [25, 26]. Consequently, uterine artery Doppler may or may not be affected in all cases. This explains why the use of uterine artery Doppler as a screening tool for PE in first trimester yields a detection rate of only 40 % and has low positive predictive values for term disease in low-risk population. However, when attention is focused on early-onset PE, uterine artery Doppler serves as an important predictor, and it is better to identify the "at risk" population in first trimester itself if the disease outcome has to be modified by adding aspirin [27]. Many studies used uterine artery Doppler measurements in the second trimester, but there is an increasing number of studies showing the effectiveness of first trimester uterine Doppler mean PI measurements [28]. Velauthar et al. [29] in their meta-analysis reviewed the accuracy of uterine artery Doppler analysis in first trimester in the prediction of FGR and PE. The predictive efficacy of uterine artery Doppler quoted is quite similar to our results.

It has been studied that women who tend to develop PE may have subtle increase in systolic blood pressure and mean arterial pressure in first and second trimester well before the onset of clinical disease [30–32]. Accurate measurements of blood pressure using a validated automatic monitor are important when attempting to identify early signs of PE. MAP is an easy, cost-effective, and noninvasive test that can readily be combined with uterine artery Doppler and maternal characteristics to improve the predictive accuracy for PE as illustrated in Table 1 under Group II.

In response to the placental hypoperfusion caused by the pathogenic placenta, various angiogenic factors are released in the maternal circulation. PAPP-A is a large glycosylated protein produced by the syncytiotrophoblast which plays an important role in fetal growth and is a known biomarker in screening for Down syndrome. In chromosomally normal pregnancies, there is evidence that low maternal serum PAPP-A is associated with increased risk for subsequent development of PE and FGR [33, 34]. About 55 % of cases with low PAPP-A value had one or more adverse outcomes, of which, 39 % were associated with low birth weight in our study. When low PAPP-A was combined with uterine PI, MAP, and maternal characteristics, the predictive efficacy for PE and FGR was fairly good. In this group, 85 % had adverse outcomes, of which, 39 % had low birth weight. Fetal loss in this group was the highest, of about 15 %.

Table 3 Case scenarios depicting follow- up of screen positive cases in various groups studied

Case	Age	History	Uterine artery PI	Risk predicted by MAP, maternal characteristics, and uterine PI	Biochemical test	Follow-up details	Outcome
1.	30	$G_3P_1L_1A_1$ G_1-3 years 2.8 kg FTND G_2-Abortion at 2 m On Aspirin	Rt. : 2.26 (87th percentile) Lt: 2.64 (>99th percentile)	MAP 1.09 MoM Risk for PE: **1:110** FGR risk: **1:92**	Not done	20 weeks: Fetal EFW < 2nd percentile Umbilical art: REDF MCA: Increased diastolic flow	IUD at 21 weeks
2.	30	$G_3P_1L_1A_1$, G_1-3 years 1.25 kg FTND, PIH G_2-Abortion Chronic hypertensive on medication. On aspirin	Rt.:1.69 (50th percentile) Lt.: 1.74 (52nd percentile)		PAPP-A: 1.01MoM PlGF screen positive Early onset PE:**1:5** Late onset PE: **1:5**	26 weeks: Fetal EFW < 2nd percentile 28 weeks: Umbilical art PI > 90th percentile CPR − 0.8 30 weeks: CPR − 0.8	Delivered 850 g baby at 30 weeks as mother developed HELPP syndrome
3.	28	$G_2P_1D_1$ G1-LSCS stillbirth 700 gm, PIH On aspirin and LMW heparin	Rt: 2.61 (>90th percentile) Lt: 2.97 (>99th percentile)	Risk for PE: **1:28** FGR risk: **1:12**	PAPP-A 0.35 MoM PlGF not done	28 weeks: Umbilical art PI > 90th percentile CPR − 0.7 29 weeks: AEDF with increased DV PI.CPR − 0.6	Loss of fetal movements at 29 weeks. Delivered 900 g baby by LSCS
4.	23	$G_3P_2L_0D_2$ G_1-LSCS at 8th month (1 kg), neonatal death, PIH G_2-LSCS-Still born at 7th month (800 gm), PIH On aspirin and LMW heparin	Rt: 1.87 (70th percentile) Lt: 3.1 (>99th percentile)		PAPP-A 1.39 MoM PlGF screen positive for Early onset PE:**1:10** Late onset PE**: 1:15**	26 weeks: Umbilical art PI > 90th percentile 33 weeks: CPR − 1.18 36 weeks: CPR − 1.0 38 weeks: CPR − 0.9.	Delivered 2.5 kg baby at 38 weeks
5.	24	Primi Came at 15 weeks	Rt: 1.03 (65th % percentile) Lt: 1.98 (>99th percentile) at 25 weeks	Not done	Not done	25 weeks: Interval growth <2nd percentile CPR − 0.9	Hypertensive from 25 weeks onwards IUD at 27 weeks

AEDF Absent end diastolic flow, *CPR* cerebroplacental ratio, *DV* ductus venosus, *EFW* estimated fetal weight, *FGR* fetal growth restriction, *FTND* full term normal delivery, *IUD* intrauterine death, *LMW* low molecular weight, *LSCS* lower segment cesarian section, *MAP* mean arterial pressure, *MoM* multiples of median, *PAPP-A* pregnancy associated plasma protein-A, *PE* pre-eclampsia, *PIH* pregnancy induced hypertension, *PlGF* placental growth factor, *REDF* reversed end diastolic flow

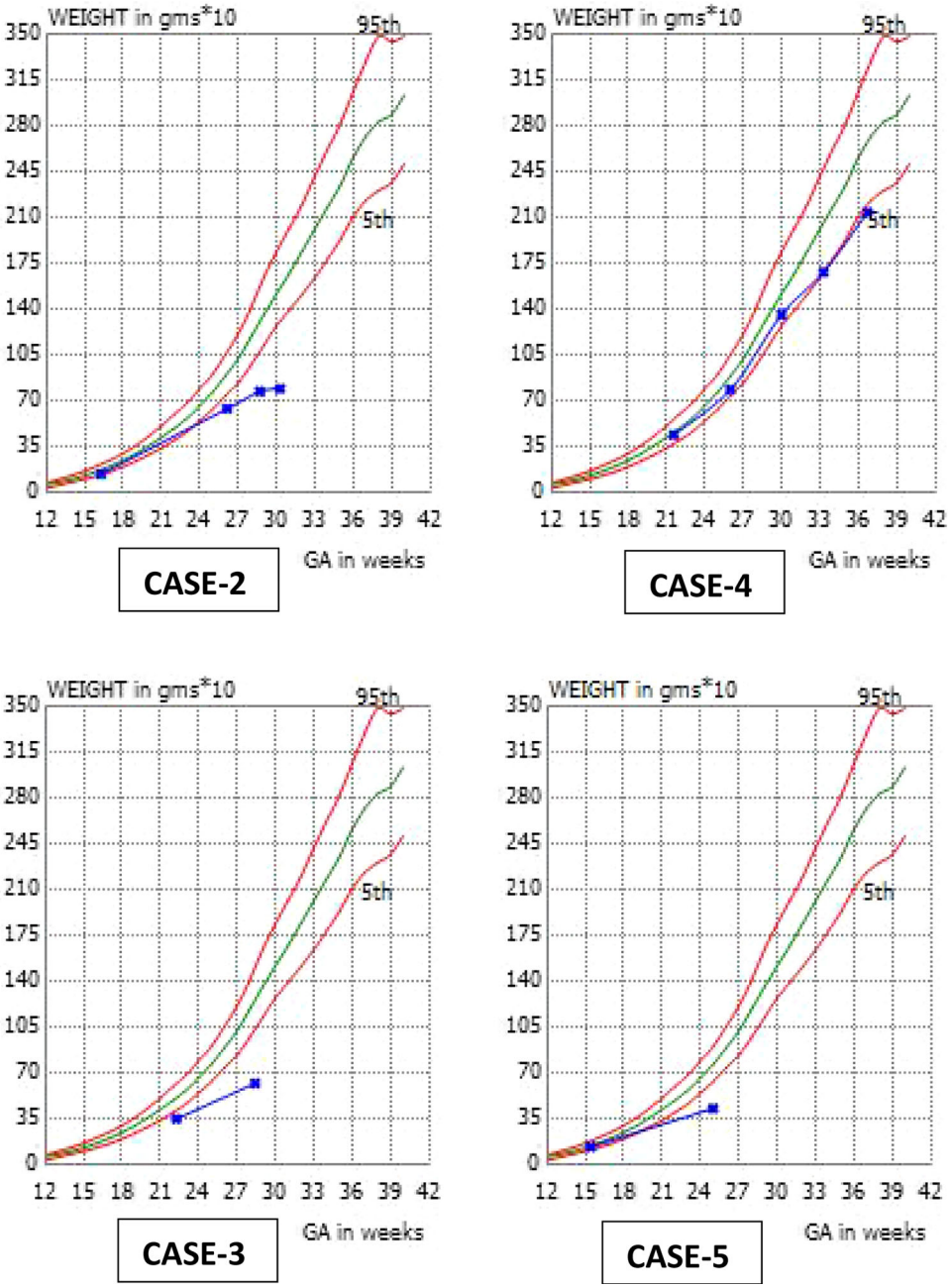

Fig. 1 Growth charts depicting interval growth in cases shown in Table 3

PlGF is secreted by developing trophoblasts and is a member of the vascular endothelial growth factor (VEGF) family. Low maternal serum PlGF levels during early gestation were associated with a significant odds ratio for development of PE ($P < .005$) [35]. Soluble fms-like tryosin kinase-1 (sFlt-1) is the spliced variant of soluble form of VEGF receptor. The level of sFlt-1 has been shown to rise significantly in serum in women who develop PE. It neutralizes PlGF and hence decreases its level [36, 37]. Cowans et al. [38] in their study showed that low levels of first-trimester PlGF provide a good indicator of small-for-gestational-age (SGA) complications, early onset PE, and HELLP syndrome.

In 400 cases, maternal history, MAP, and uterine artery Doppler were taken into consideration along with PAPP-A and PlGF, and risk prediction was done for early and late onset PE. All the 23 cases that were screen positive for early onset PE had one or more adverse outcomes making PlGF the most sensitive test for detecting early onset PE. The predictive accuracy was not as good for late onset PE as shown in Table 2. Maternal hypertension was best predicted with PlGF as 65 % of women in the early onset

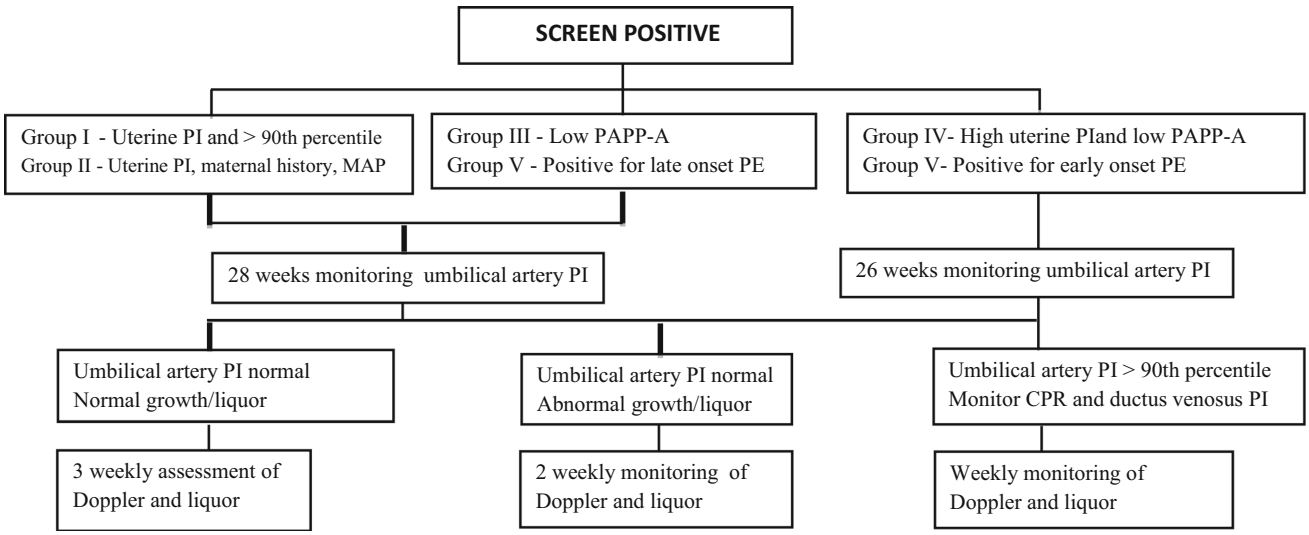

Fig. 2 Flowchart illustrating ultrasound surveillance in screen positive cases

group and 55 % in the late onset group developed hypertension.

Few case scenarios are illustrated in Table 3. The woman had a fetal loss at 22 weeks and had high uterine artery PI in Case 1. Also, she was screen positive, the risk for PE being 1:110 and for FGR being 1:92. Given the common origins of FGR and PE in defective placentation and consequent uteroplacental insufficiency, fetal compromise was evident early in gestation at 20 weeks. Case 2 shows the significance of PlGF testing in a known hypertensive patient to predict superimposed PE. Case 3 belonged to Group IV. The woman had high uterine artery PI, the risk for PE being 1:28, for FGR being 1:12 and had a low PAPP-A of 0.35 MoM. This case was on prophylactic low molecular weight (LMW) heparin and aspirin based on her history even before screening had been done. Enhanced surveillance in this case helped us to identify fetal compromise at 29 weeks and a live baby weighing 900 g was delivered. Case IV represents a scenario wherein appropriate screening, prophylactic therapy, and timely intervention resulted in a fruitful outcome in a high-risk case. Case 5 depicts a scenario in which, screening during first trimester was not done and the mother was hypertensive from 25 weeks onwards, ended up in IUD at 27 weeks. Growth charts of these cases are illustrated in Fig. 1.

This study also emphasizes the need for increased surveillance in the screen positive group. We had devised a protocol based on the number of screen positive parameters present to monitor these cases as shown in Fig. 2. Serial assessment of fetal growth using growth charts, liquor status, umbilical artery PI, and cerebroplacental ratio were used for surveillance in these cases. In early onset uteroplacental insufficiency, there is an increase in umbilical artery PI early in gestation and the progression to absent end diastolic flow (AEDF) and reversed end diastolic flow (REDF) occurs rapidly and hence, this group had to be kept under strict surveillance.

This study is one of the first of its kind in the Indian population and throws light on the presence of adverse outcomes when one or more screening parameters are positive for PE. The study included both the high-risk group who had already been on prophylactic aspirin based on history and also the low-risk cases. The study having been done in the rural setup, our referring clinicians were unable to offer the ideal screening test for all the cases due to economical constraints, which is actually the real life scenario. Our study plots the predictive efficacy for individual screening parameter and also for a few in combination so that with the available resources in a particular locality, one can still try to offer screening for PE considering the severe consequences of the disease. A slightly higher false positive rate for PE would generally be of no great harm for the screen positive cases would just be offered prophylactic aspirin and enhanced surveillance [39].

Conclusion

Evolving through the years with an aim of constant improvement and better healthcare, we have achieved many milestones. Down's screening during first trimester, which used to be done only among high-risk women, has now come into the gamut of routine antenatal care. Hence, the utility of 12 weeks scan and the biomarkers for aneuploidy screening can aptly be used for PE screening as well

with no additional cost to the patient. Incidence of Down syndrome is 1:700, whereas early onset PE is three and half times more prevalent being associated with 1:200 pregnancies. Hence, screening for PE and FGR should be universal and not be confined to only the high-risk population. The rationale for screening in early gestation is to predict later pregnancy complications which allows for the early commencement of proven prophylactic therapy and to enhance clinical surveillance in the truly high-risk population. No later pregnancy complications can be predicted with sufficient specificity and sensitivity by a single biomarker and hence, multiparametric testing is required to achieve adequate predictive performance. Though the motive is implementation of the best screening test to the whole population, inability to do so must not stop one from offering PE screening. In the current scenario, even a part of the screening protocol including few parameters like uterine Doppler, maternal characteristics, MAP, or PAPP-A might improve our screening potential for PE and FGR, which would definitely aid in our venture to minimize adverse perinatal outcomes.

Compliance with Ethical Standards

Conflict of interest None.

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