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Original Research Article

Study of fetomaternal arterial doppler parameters in early onset pre-eclampsia and its correlation with perinatal outcomes

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ABSTRACT

Background: Development of pre-eclampsia (PE) at less than 34 weeks of gestation is known as early onset PE (EOPE) and is commonly associated with more severe adverse maternal and fetal outcomes. The purpose of this study was to study Doppler parameters of uterine, umbilical and fetal middle cerebral arteries exclusively in women with EOPE and its correlation with perinatal outcomes. This study was a hospital-based observational prospective study.
Methods: 60 patient of early onset PE with singleton live pregnancy were included in the study and followed up. The results of sonographic and Doppler examination were analysed and correlated with perinatal outcomes.
Results: Adverse perinatal outcomes were seen in 66.66% cases of early onset PE. To predict adverse perinatal outcomes, umbilical artery (Umb A) RI, PI were found to be most sensitive, cerebroplacental ratio (CPR) was most specific indicator with highest positive predictive value (PPV). Absent end diastolic flow /reverse end diastolic flow (AEDF/REDF) were ominous signs.
Conclusions: Early onset PE is recently considered a more severe disease with different etiopathogenesis. Doppler study is the primary imaging modality for fetomaternal surveillance for follow up and prediction of perinatal outcome, thus allowing planning of timely management in early onset PE patients, as these patients are at higher risk of adverse perinatal outcomes.

Keywords: Cerebroplacental ratio, Early onset pre-eclampsia, Middle cerebral artery, Umbilical artery, Uterine artery

INTRODUCTION

Pre- eclampsia (PE) is a multisystem disorder of unknown etiology, associated with raised blood pressure and proteinuria and remains a major cause of morbidity and mortality. PE developing before 34 weeks of gestation is known as early onset PE (EOPE) and should be regarded as different form of the disease as these patients are at higher risk for maternal and perinatal adverse outcome.[1] Leading hypotheses suggest that reduced uterine perfusion in late gestation leads to placental ischemia, which results in release of placental factors and maternal endothelial dysfunction subsequently, ultimately resulting in fetomaternal co-morbidities.[2]

The main objective of antenatal care in EOPE patients is the accurate detection of the compromised IUGR fetus, to allow for timely intervention. The most common methods used currently for antenatal surveillance are biophysical profile (BPP) and non-stress test (NST), neither of these tests is particularly sensitive for predicting poor outcome in compromised intra uterine growth restriction (IUGR) pregnancies. Doppler velocimetry can be used as a better tool for antenatal fetal surveillance, since it is a non-invasive test, easy to perform, interpret and significantly predicts the fetal status in utero and its perinatal outcome. Most of the Doppler studies have been done in pregnancy induced hypertension (PIH) patients or PE patients and are focused on umbilical artery (Umb A) Doppler parameters. Only few studies have been done exclusively on early

onset preeclampsia patients.[3] The present study focused exclusively on EOPE patients, a severe form of the disease carrying higher risk of poor perinatal outcomes and highlights the significance of Doppler sonographic changes in Umb A as well as middle cerebral artery (MCA) and uterine artery (Ut A) and their combined parameters, cerebroplacental ratio (CPR) for early detection of fetal complications, enabling better planning of management decisions and monitoring strategy for these high-risk patients.

METHODS

This was a tertiary hospital-based observational prospective study, conducted in the department of Radio diagnosis, Lady Hardinge Medical College and associated Smt. Sucheta Kriplani Hospital and Kalawati Saran Children Hospital, New Delhi, India from December 2017 to March 2019. 60 patients of early onset pre-eclampsia with singleton live pregnancy and with known last menstrual period (LMP) or gestational age confirmed by 1st trimester scan were studied and followed up till their stay in hospital post-delivery. For this study, PE was defined as elevated blood pressure ≥140/90 mmHg on two measurements 6 hours apart and proteinuria >30 mg in a 24 hours urine sample or at least 1+ in a dipstick random urine sample, in pregnancy after 20 weeks of gestational age.[4]

Pregnancies with multiple gestation, fetal anomalies, diabetes mellitus, chronic renal diseases, chronic hypertension, chronic liver disease, APLA syndrome, patients requiring immediate treatment and patients not giving consent to participate in the study were excluded.

Ultrasound scanning

A routine antenatal sonography was performed on IU22-PHILIPS using 3.5 MHz convex transducer. After ensuring single live intrauterine pregnancy, the lie and presentation were determined. Placental location and grade was observed. The fetal biometry parameters including biparietal diameter (BPD), head circumference (HC), femur length (FL) and abdominal circumference (AC) were recorded. Amniotic fluid index (AFI) was determined by dividing the uterus into four quadrants by sagittal and transverse lines through the umbilicus and summing the vertical dimensions of the deepest pocket of each quadrant. AFI <8 cm, was considered oligohydramnios and >20 cm was considered as polyhydramnios. Estimation of fetal weight was done using Hadlocck's regression equation (1984) including all four parameters BPD, HC, AC and FL.

Doppler velocimetry

The Doppler examination was done at the time of admission and was repeated whenever required. The examination was done on PHILIPS IU22 using a 3.5 MHz curvilinear probe. The maternal uterine and fetal vessels were insonated keeping the angle <60° between ultrasound beam and direction of blood flow. Measurements were taken during fetal apnoea and no body movements. After obtaining a good quality signal, peak systolic and end diastolic frequency shifts were recorded. The signal was updated until 3 consecutive waveforms were obtained.

Uterine artery: The transducer was placed 2-3 cm medial to anterior superior iliac spine, directing the ultrasound beam to the lateral wall of the uterus and slightly downwards towards the pelvis. Colour flow imaging was used to identify the uterine artery at a point of apparent "cross-over" with external iliac artery keeping the angle of insonation <60°, uterine artery wave form was recorded on both sides.

The flow velocity waveform of uterine artery was considered abnormal if there was persistent early diastolic notching beyond 24 weeks of gestation and/or if the resistivity index (RI), pulsatility index (PI) or systolic/diastolic (S/D) ratio was >95th percentile.[5]

Umbilical artery: Umbilical artery recordings were taken from a free-floating part of loop, keeping the angle of insonation <60°.

Umb A Doppler parameters were considered abnormally high if values were higher than 95th percentile for the gestational age.[6]

Middle cerebral artery: The transducer was focused in a trans axial plane (at the level of BPD) and the artery was identified in close proximity to the greater wing of sphenoid between anterior and middle cranial fossa. Doppler waveforms were obtained from the proximal part of MCA.[7]MCA PI, RI and S/D ratio were considered abnormal if values were <5th percentile.[8]

Cerebroplacental ratio: It was calculated as PI of middle cerebral artery divided by PI of umbilical artery and a ratio of <1.08 was taken as abnormal.

Follow up of patients

Patients were admitted to the maternity ward and were started on treatment or kept under observation until termination of pregnancy. Follow up Doppler studies were performed as required to determine and monitor foetal well-being status till delivery or termination of pregnancy, however only the results of 1st Doppler study were used for statistical evaluation and deriving results.

Peri natal outcomes

Adverse outcome included the following outcome variables: 1) intrauterine death (iud), 2) still birth, 3) need for resuscitation at birth, 4) need for positive pressure ventilation, 5) APGAR score at 5 minutes <7, 6) low birth weight, 7) pre term, 8) neonatal ICU (NICU) admission, 9) duration of stay in NICU.

Statistical evaluation

The data generated from our research study was analysed using SPSS (version 25). Categorical data was expressed as proportions. For quantitative data, mean and standard deviation were calculated analysis of variance/Chi square test and Multiple regression analysis were applied for comparison of perinatal outcome in various groups. 'p' value of <0.05 was considered as statistically significant and 'p' value <0.01 was considered as highly significant. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated.

RESULTS

The results are presented in the form of tables and figures. On the basis of arterial Doppler velocimetry (normal Doppler velocimetry or single/two/three vessel) abnormality all 60 cases in our study were categorized into 5 groups (Figure 1).

In group 1 (normal Doppler velocimetry) no adverse perinatal outcome was noted. In group 2 [single vessel (Ut A only) abnormality], NICU admission was required for 11% cases, while 22% cases resulted in preterm delivery and 33% babies were low birth weight. In group 3 [single vessel (Umb A only) abnormality] NICU admission was required for 42.8% cases, 42.8% cases resulted in preterm delivery, 57% babies were low birth weight. The incidences of adverse perinatal outcome were more compared to only uterine artery involvement. In group 4 [two vessel (Umb A and Ut A) abnormality] maximum number of patients (53.3%) in our study belonged to this group, perinatal mortality was observed in 21.8% cases, 65.6% cases required NICU admission, 78% cases resulted in preterm and low birth weight babies. In group 5 [all three vessels (Umb A and Ut A and MCA) abnormality] worst perinatal outcomes were noted in this group. 60% perinatal mortality, 80% NICU admission and 100% cases resulted in preterm and low birth weight (LBW) babies, out of which 80% were extremely low birth weight (ELBW) babies.

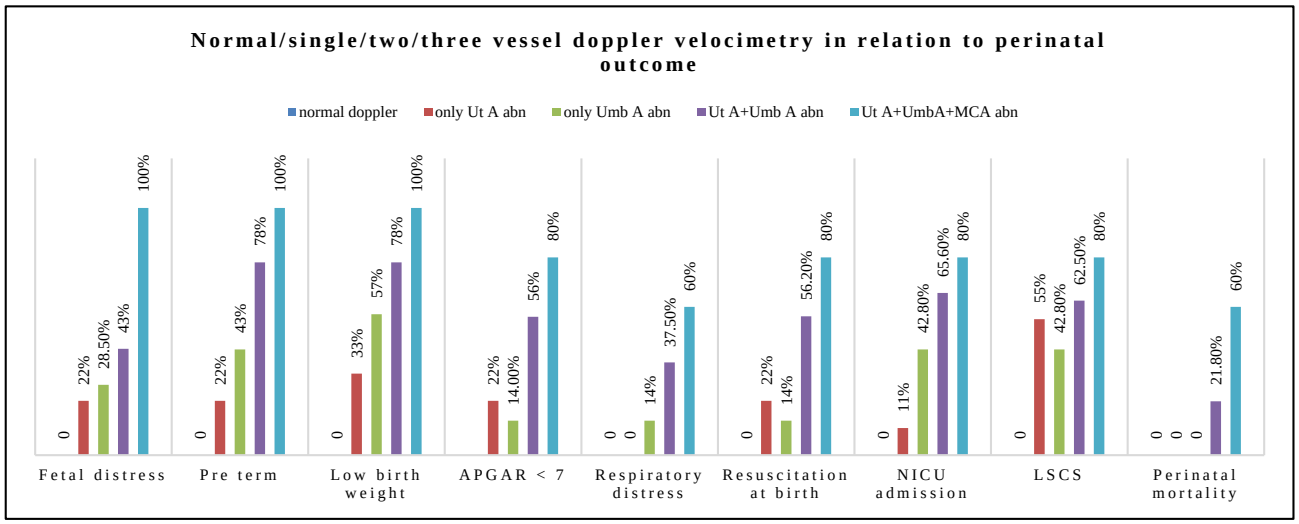

Figure 1: Distribution of various perinatal outcomes amongst the 5 groups based on normal/single/two/three vessel Doppler abnormality.

Table 1: Efficacy of doppler parameters in predicting adverse perinatal outcomes.

Doppler findings	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy	P value
Umb A RI	90.0%	60.0%	81.8%	75.0%	80.0%	<0.001
Umb A PI	90.0%	60.0%	81.8%	75.0%	80.0%	<0.001
Umb A S/D	87.5%	60.0%	81.4%	70.6%	78.3%	<0.001
MCA RI	12.5%	100.0%	100.0%	36.4%	41.6%	0.143
MCA PI	10.0%	100.0%	100.0%	35.7%	40.0%	0.143
MCA S/D	10.0%	100.0%	100.0%	35.7%	40.0%	0.143
CPR	57.5%	85.0%	88.5%	50.0%	66.6%	0.002
UTA RI	90.0%	50.0%	78.3%	71.4%	76.7%	0.001
UTA PI	87.5%	50.0%	77.8%	66.7%	75%	0.002
UTA S/D	90.0%	50.0%	78.3%	71.4%	76.7%	0.001
NOTCH UTA	82.5%	70.0%	84.6%	66.7%	78.3%	<0.001

Table 2 Comparison of efficacy of umbilical artery RI in predicting adverse perinatal outcome.

Umb A RI	Gaikwad et al[12]	Konwar et al[15]	Lakhkar et al[14]	Present study
Sensitivity	37.84%	60.6	44.4%	90%
Specificity	79.71%	70.6	81.8%	60%
PPV	50%	80.0	80%	81.8%
NPV	70.51%	48.0	47.3%	75.0%
Diagnostic accuracy	65.09%	64.0	68.9%	80.0%

Table 3: Comparison of efficacy of umbilical artery PI in predicting adverse perinatal outcome.

Umb A PI	Gaikwad et al[12]	Smitha et al[11]	Lakhkar et al[14]	Konwar et al[15]	Present study
Sensitivity	29.73%	90.26%	58%	60.6%	90%
Specificity	92.75%	80.57%	56.5%	58.5%	60%
PPV	68.75%	82.24%	35%	74.1%	81.8%
NPV	71.11%	88.35%	86.8%	43.5%	75.0%
Diagnostic accuracy	70.75%	84%	56.8%	60.0%	80.0%

Table 4: Comparison of efficacy of umbilical artery S/D ratio in predicting adverse perinatal outcome.

Umb A S/D ratio	Gaikwad et al[12]	Konwar et al[15]	Lakhkar et al[14]	Present study
Sensitivity	40.54%	75.8%	75%	87.5%
Specificity	89.86%	41.2%	41.3%	60%
PPV	68.18%	71.4%	25%	81.4%
NPV	73.81%	46.7%	86.3%	70.6%
Diagnostic accuracy	72.64%	64.0%	48%	78.3%

Table 5: Comparison of efficacy of cerebroplacental ratio (CPR) in predicting adverse perinatal outcome.

Cerebroplacental ratio (CPR)	Padmini et al[10]	Smitha et al[11]	Konwar et al[15]	Gaikwad et al[12]	Lakhkar et al[14]	Present study
Sensitivity	88%	94.4%	84.8%	45.9%	47.2%	57.5%
Specificity	91%	82.6%	76.5%	98.5%	86.3%	85%
PPV	78%	86.4%	87.5%	94.4%	85%	88.5%
NPV	73%	96.4%	76.2%	77.2%	50%	50%

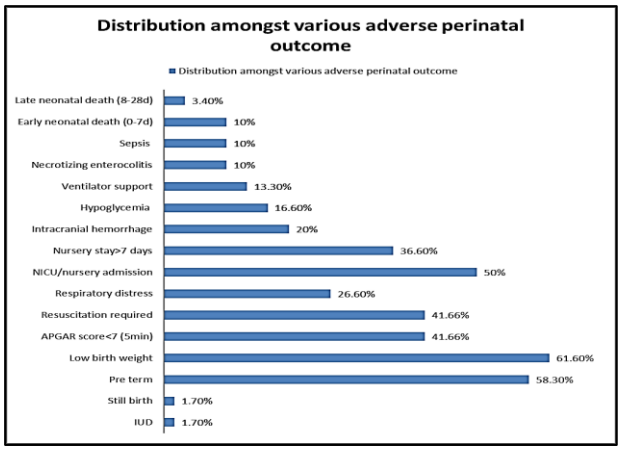

Figure 2: Distribution amongst various adverse perinatal outcomes.

The percentage of adverse perinatal outcome increased as number of vessels showing abnormal Doppler velocimetry increased. Highest sensitivity for predicting adverse perinatal outcome was observed with umbilical artery RI, PI and uterine artery RI and S/D ratio (90%) (Tables 1-3). Highest specificity for predicting adverse perinatal outcome was seen with CPR (85%) followed by Ut A diastolic notch (70%) (Table 1). Highest PPV for predicting adverse perinatal outcome was also noted with CPR (88.5%) followed by diastolic notch in uterine artery (84.6%) (Table 1). Highest negative predictive value (NPV) for predicting adverse perinatal outcome was also seen with Umb A RI, PI (75%) (Table 1). Overall highest diagnostic accuracy was noted with Umb A RI and PI (80%) (Table 1).

DISCUSSION

With advancing gestation, Umb Doppler waveforms demonstrate a progressive rise in the end-diastolic flow and a decrease in the impedance indices, while brain is the area of high vascular impedance with continuous forward flow throughout cardiac cycle in 2nd and 3rd trimester in

normal developing foetuses.[9] Umb A Doppler parameters are considered as an index of resistance to flow in fetoplacental circulation and correlates well with fetal hypoxia and acidosis. In EOPE, as the placental insufficiency worsens, the diastolic flow in Umb A decreases, then become absent, and later reverses (Figure 3).

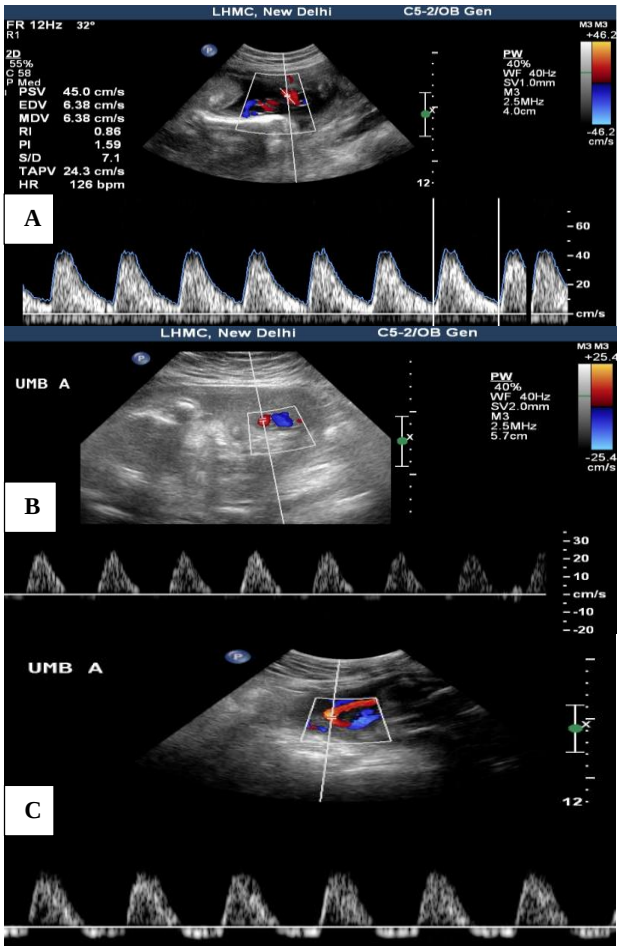

Figure 3: A) Umb A flow waveform showing markedly reduced diastolic flow with increased resistance RI (0.86), PI (1.59) and S/D ratio (7.1); B) Umb A flow waveform showing absent end diastolic flow (AEDF); C) umbilical artery flow waveform showing reversal of end diastolic flow (REDF).

In our study, Umb A RI and PI showed high sensitivity (90%), PPV (81.8%) and diagnostic accuracy (80%) in predicting adverse perinatal outcome in patients with EOPE, these results are in line but comparatively high with the studies done by Padmini et al and Lopez Mendez et al in PE patients and Smitha et al and Gaikwad et al in PIH patients.[10-13] Similarly in a study by Lakhkar et al, high PPV (80%) was observed for Umb A RI in predicting adverse perinatal outcome in patients with PIH and IUGR, these findings are in agreement with our study.[14]

S/D ratio of umbilical artery also show sensitivity, specificity, PPV, NPV and diagnostic accuracy of 87.5%, 60%, 81.4%, 70.6% and 78.3% respectively in predicting adverse perinatal outcome in early onset preeclampsia patients but less sensitive as compared to Umb A RI and PI. Similar findings in agreement with our study were noted in the study done by Lakhkar et al and Konwar et al in PIH patients but were low as compared to our study for predicting adverse perinatal outcome.[14,15]

Results show all patients with AEDF/REDF resulted in early pre term birth and low birth weight, poor APGAR score, large numbers of NICU admission (93.7% cases) and increased need for positive pressure ventilation during NICU stay (43.7% cases). Also, higher incidence of babies developing sepsis (31.2%), intraventricular haemorrhage (50% cases), necrotizing enterocolitis (37.5% cases), IUD and neonatal death were noted in patients with AEDF/REDF, making them ominous signs during ANC Doppler surveillance. Findings consistent with our study were observed in the study by Gaikwad et al and Lakhkar et al but incidences were higher in our study likely because EOPE is more severe disease and carry higher risk for perinatal adverse outcomes.[13,14]

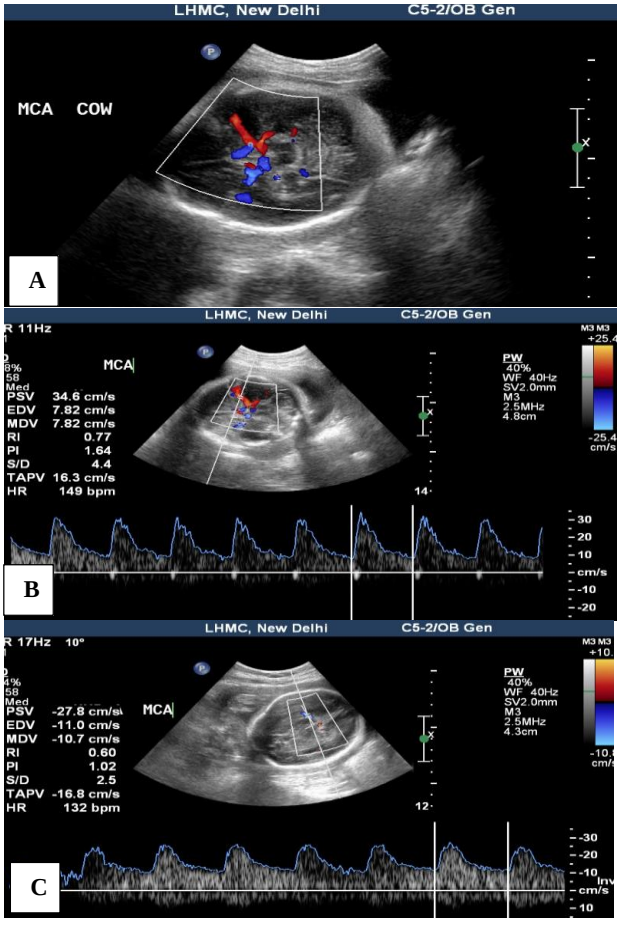

Figure 4: A) Circle of Willis shown on color Doppler imaging, anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA); B) MCA flow velocity waveform showing normal high resistance flow pattern; C) increased flow in MCA indicative of fetal compromise- abnormal MCA PI (1.02) sign of 'brain sparing effect'.

CPR showed highest specificity (85%) and PPV (88.5%) with diagnostic accuracy of 66.6%. However, sensitivity and NPV were low 55.7% and 50% respectively were low as compared to umbilical artery RI, PI and S/D ratio for predicting adverse perinatal outcome in EOPE patients. Results of our study are in agreement with Gaikwad et al, Lakhkar et al, Konwar et al and Regan in severe PE patients, showing high specificity and PPV for CPR.[13-16]

In our study 8.3% cases showed abnormally low resistance MCA Doppler parameters signifying fetal brain sparing effect (fetus redistributes its cardiac output to maximise oxygen and nutrient supply to the brain) (Figure 4) as demonstrated by Konwar et al and Cohen et al MCA PI, RI and S/D ratio showed 100% specificity and PPV with diagnostic accuracy of 40%, but couldn't reach statistical significance as p value was 0.143 for predicting adverse perinatal outcome (Figure 4).[15,17] To increase sensitivity of MCA Doppler parameters, serial Doppler examinations of MCA in combination of umbilical artery are required so that fetal decompensation cases are not missed out, where MCA Doppler velocimetry starts increasing just before fetal demise.

The results of our study are in line but comparatively high with all the previously mentioned studies, likely because those studies were done in PIH patients or PE patients in general, however our study specifically focuses EOPE which is recently considered a severe disease with different etiopathogenesis.[18] EOPE is considered a fetal disorder that is typically associated with placental dysfunction, reduction in placental volume, multiorgan dysfunction and severe adverse maternal and neonatal outcomes, however Late-onset PE is considered a maternal constitutional disorder, associated with a normal placenta and more favourable maternal and neonatal outcomes.[19]

In our study sample size was small, same study can be done on a big sample size for better external validity. Deranged MCA should be serially followed on regular interval not to miss out on MCA decompensation cases.

CONCLUSION

In patients with EOPE and abnormal Doppler parameters, pregnancy outcome was poor compared to patients with normal Doppler velocimetry. The proportion of cases with adverse perinatal outcomes increased as number of vessels with abnormal Doppler parameters increased. To predict adverse perinatal outcome, Umb A RI, PI, Ut A RI and S/D ratio were found to be most sensitive, while CPR was the most specific parameter with highest PPV, followed by Ut A diastolic notch. NPV and diagnostic accuracy was maximum with umbilical artery RI and PI. AEDF/REDF were ominous sign, 100% cases resulted in preterm delivery and low birth weight, 93.7% cases required NICU admission and 50% cases resulted in perinatal mortality. We conclude that Doppler study is the primary imaging modality of choice for fetomaternal surveillance in early onset preeclampsia patients, as these patients are at a higher risk of adverse perinatal and maternal outcome. Doppler study helps us to follow up, predict perinatal outcome, take timely action and plan the correct management.

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