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## Original Research Article

# Correlation of longitudinal changes that occur in fetal middle cerebral artery-peak systolic velocity with middle cerebral artery-pulsatility index in late onset intrauterine growth restriction cases

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## ABSTRACT

**Background:** Fetal blood flow can be studied by Doppler patterns which follow a longitudinal trend with sequential changes in umbilical artery, middle cerebral artery followed by other peripheral arteries. Though FGR cannot be treated but morbidity and mortality can be decreased by studying longitudinal changes in MCA-PI (middle cerebral artery-pulsatility index) and MCA-PSV (middle cerebral arterial-peak systolic velocity) and terminating the pregnancy at appropriate time.

**Methods:** A prospective observational study was conducted from 2018 to 2019 on 29 antenatal patients with suspicion of fetal growth restriction at  $\geq 32$  weeks gestation. Patients with late onset FGR by Delphi procedure with singleton pregnancy and confirmed gestational age were included. Patients with gross congenital anomaly or multiple pregnancy were excluded. Peak systolic velocity, resistance index and PI in middle cerebral artery were recorded in absence of fetal movements. MCA-PSV  $>95$ th percentile and MCA-PI  $<5$ th percentile for that gestational age were considered abnormal. The compiled data was subjected to statistical analysis.

**Results:** Mean gestational age was  $36.28 \pm 1.6$  weeks at enrolment and  $36.65 \pm 1.56$  weeks at delivery. The longitudinal changes in MCA-PSV values showed an increase in all the patients but in 11 patients, it was abnormal and out of these there was fall in 6 patients after an increase. MCA-PSV fall was strongly associated with perinatal mortality (p value 0.0003 and kappa 0.664). In 22 patients with increase in MCA-PSV there was decrease in MCA-PI while in 7 patients MCA PI increased which could be due to pseudo normalization phenomenon due to cerebral oedema. Association of MCA-PSV fall with adverse perinatal outcome was not significant (p value  $>0.05$ ). The sensitivity of MCA-PSV fall in predicting the perinatal mortality was 80% and specificity was 91.76%.

**Conclusions:** MCA-PSV not only complements MCA-PI but also provides more accurate information than does MCA-PI alone and should be used along with MCA-PI for optimizing fetomaternal outcome.

**Keywords:** MCA-PSV fall, MCA-PI, Late onset IUGR, Perinatal outcome

## INTRODUCTION

Intrauterine growth restriction (IUGR) is a pathological condition in which a foetus has not achieved its genetic growth potential; regardless of its size.<sup>1</sup> It is a common and

complex obstetric problem which affects approximately 10-15% of pregnant women.<sup>2</sup>

Low birth weight (LBW), small for gestational age (SGA), IUGR or fetal growth restriction (FGR) are applied in an

inconsistent and confusing manner but they are not synonymous. The term IUGR or FGR are similar and should be used only in regard to fetus whereas SGA should be used mainly in new born whose birth weight is below the tenth percentile for the appropriate gestational age. SGA may be labeled according to reference population standards if the newborn is constitutionally small but otherwise normal (e.g. born to parents who are small and/or into an ethnic population that is smaller than the reference population). Alternatively, a fetus with delayed growth late in gestation may not have a reduction in birth weight significant enough to be classified as SGA.<sup>3</sup>

For the achievement of a normal pregnancy, development of a good utero-placental circulation is essential, for which remarkable changes occur in the maternal, placental and fetal vasculature. Fetuses that are growth-restricted, secondary to placental insufficiency redistribute their blood flow from periphery to the brain also known as the brain sparing effect.<sup>4</sup> When this mechanism fails, abnormal vascular resistance patterns develop which lead to compromise of fetal well-being, with a six to ten time higher risk of perinatal mortality.<sup>4,5</sup>

The diagnosis of IUGR/FGR is usually made clinically in the antenatal period however biometry and Doppler (arterial and venous) by ultrasound examination are essential for diagnosis and follow up. An estimated fetal weight (EFW) or AC below 10th percentile raised concerns of a suboptimal intrauterine growth, however the distinction between normal and pathologic growth often cannot reliably be made at this arbitrary cut off.<sup>6</sup> In addition, approximately 70% of fetuses below the 10th percentile had normal perinatal outcome by Lees et al 2013.<sup>5</sup> Thus it was always a challenge to obstetrician to identify the pathological fetal growth restriction in order to allow intervention that would decrease perinatal morbidity and mortality.

Fetal blood flow can be studied by Doppler patterns which follow a longitudinal trend with sequential changes in umbilical artery, middle cerebral artery followed by other peripheral arteries. If adequate measures are not taken at this point venous changes appear in the severely compromised fetus. Doppler studies reveal changes of hypoxia at least one week before the non-stress test or the biophysical profile.<sup>7</sup> Venous changes are often late and are signs of advanced fetal compromise and are usually associated with the presence of acidemia.<sup>7</sup> In early onset IUGR (<32 weeks of gestation) the sequence of changes in Doppler has been studied very well but in late onset IUGR ( $\geq 32$  weeks of gestation) the longitudinal changes in Doppler studies have not been investigated.<sup>3</sup>

Very few studies have been done to show longitudinal changes occurring in MCA-PI and MCA-PSV in IUGR fetuses.<sup>3,6,8</sup> Though FGR cannot be treated but morbidity and mortality can be decreased in the baby by terminating the pregnancy at appropriate time. So, the present study

was aimed to measure the longitudinal changes occurring in MCA-PI and MCA-PSV in late onset IUGR fetuses ( $\geq 32$  weeks) and if they could be used for predicting the timing of delivery. Also to study if these longitudinal changes in middle cerebral artery Doppler could help in assessing the fetal well-being and predicting the fetal outcome in late onset IUGR pregnancies?

## METHODS

This was a tertiary care hospital based prospective observational study conducted from 2018 to 2019 on 29 antenatal patients with clinical suspicion of FGR presenting at  $>32$  weeks period of gestation in the department of obstetrics and gynecology, Hindu Rao hospital and NDMC medical college, North DMC, Delhi, in close association with department of radiology and pediatrics. Fetal growth restriction was suspected clinically when there was a discrepancy of 3 weeks or more between period of gestation and symphysio fundal height. Patients with singleton pregnancy with confirmation of gestational age either by surety of dates or by early first trimester USG and fitting in the category of late onset FGR were included in the study. Late onset IUGR is defined as a fetus at  $\geq 32$  weeks period of gestation in absence of congenital anomalies with AC/EFW  $<3$ rd percentile as single criterion or at least two out of three: abdominal circumference (AC)/effective fetal weight (EFW)  $<10$ th percentile; AC/EFW crossing percentiles  $>2$  quartiles on growth percentiles; or CPR  $<5$ th percentile or UA-PI  $>95$ th percentile which was on the basis of definition given by latest consensus (2016) among senior specialist worldwide by using Delphi procedure.<sup>9</sup>

Patients with gross congenital anomaly or with presence of USG soft markers showing suspicion of any karyotype abnormality in fetus or with multiple pregnancy were excluded from the study. All patients fulfilling the inclusion criteria were taken up for the study once they had given written informed consent. Menstrual history or any significant past medical or surgical history, dietary, personal or family history was obtained. A general physical and obstetric examination was performed.

Doppler studies were done by trans-abdominal method. Vessels were identified by color Doppler and spectral trace was obtained from umbilical and middle cerebral arteries. The parameters like peak systolic velocity (PSV), RI and PI in middle cerebral artery were recorded. All recordings were obtained in the absence of fetal breathing and fetal movements.

Doppler studies were repeated weekly or every 2nd or 3rd day depending upon the period of gestation whenever high resistance was seen in umbilical artery. Patients were monitored longitudinally and steroid coverage was given for fetal lung maturity whenever required. The MCA-PSV were considered abnormal if the measurements was above the upper limit of normal ( $>95$ th percentile for the

gestational age) and the MCA-PI was considered abnormal if the measurements was below the lower limit of normal (<5th percentile for the gestational age), according to available nomograms for that period of gestation, as given by Doppler calculator. Available at <https://medicinafetalbarcelona.org/calc/2017.10>.

Management of the patients was done as per standard hospital protocol. They were followed till delivery for various fetomaternal outcomes. Adverse perinatal outcome included intrauterine death, stillbirth, early neonatal mortality or neonatal complication like hypoglycemia, sepsis, seizures and stay in NICU.

The data was compiled and subjected to statistical analysis using statistical package for social sciences (SPSS) version 21.0. Privacy and confidentiality of each participant was assured.

## RESULTS

The mean age of patients with pregnancy with IUGR in our study was 24.97 years and ranged from 19 to 32 years.

62% patients were nulliparous and majority of them (41.4%) were educated up to 10th class or more. Mean gestational age at the time of enrolment was 36.28±1.6 weeks and 36.65±1.56 weeks at delivery with range from 32 to 39 weeks at delivery.

In 29 patients serial Doppler were done (26 patients had 2 Doppler readings and 3 patients had 3 Doppler readings) and they were studied for the longitudinal changes in MCA-PSV and MCA-PI. We found that there was an increase in values for MCA-PSV in all the patients but in 11 patients, it was abnormal (>95th percentile) and out of these there was fall in MCA-PSV in 6 patients after showing an increasing trend (Table 1). Longitudinal changes in MCA-PSV and MCA-PI with MCA PSV fall in 3 patients are shown along with final consequences (Figure 1-3). In 22 patients when MCA-PSV increased there was decrease in MCA-PI. But in 7 patients when MCA-PSV increased there was an increase in MCA PI (longitudinal changes in 2 patients shown in Figure 4 and 5). The fetomaternal outcome and birth weight in these patients has been mentioned in the individual graphs.

**Table 1: Distribution of patients of late onset IUGR according to various Doppler parameters at last scan.**

Doppler parameters of vessels	Number of patients (n=29)	Percentage (%)
<b>MCA-PI</b>		
Normal (≥5th percentile)	18	62.07
Abnormal (<5th percentile)	11	37.93
<b>MCA-PSV</b>		
Normal (<95th percentile)	18	62.07
Abnormal (≥95th percentile)	11	37.93

**Table 2: Correlation of MCA-PSV fall with perinatal mortality.**

Correlation		Perinatal mortality		Total	P value <sup>1</sup>	Kappa
		No	Yes			
		N (%)	N (%)	N (%)		
MCA-PSV fall	Absent	22 (75.86)	1 (3.45)	23 (79.31)	0.0003	0.664
	Present	2 (6.90)	4 (13.79)	6 (20.69)		
<b>Total</b>		24 (82.76)	5 (17.24)	29 (100.00)		

<sup>1</sup>Chi square test.

**Table 3: Correlation of MCA-PSV fall with adverse perinatal outcome in patients with late onset IUGR.**

Doppler parameter		Adverse perinatal outcome		Total	P value
		Yes	No		
MCA PSV fall n=29	Absent	19	4	23	0.553#
	Present	6	0	6	
<b>Total</b>		25	4	29	

#Fisher exact test.

**Table 4: MCA-PSV fall and its predictive value for perinatal mortality and adverse perinatal outcome.**

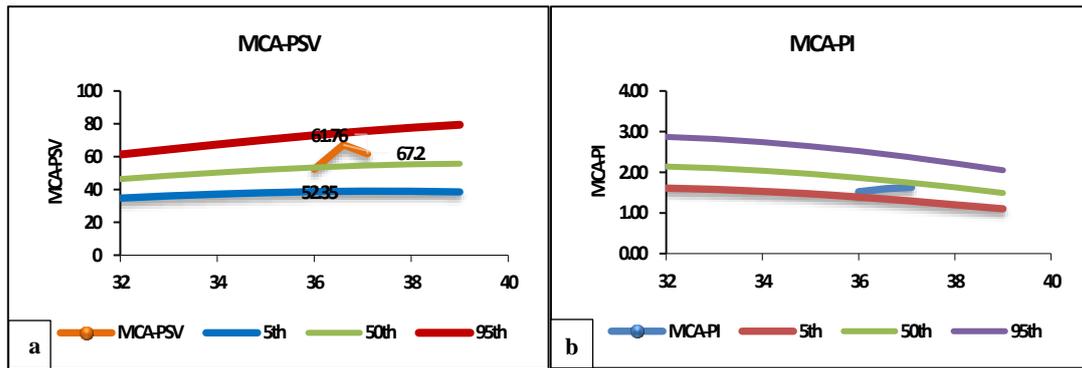
MCA-PSV fall	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	NPV (%)	P value
<b>Perinatal mortality</b>	80.00	91.67	0.86	66.67	95.65	0.00031
<b>Adverse perinatal outcome</b>	24.00	100.00	0.62	100.00	17.39	0.553#

#Fisher exact test; <sup>1</sup>Chi square test.

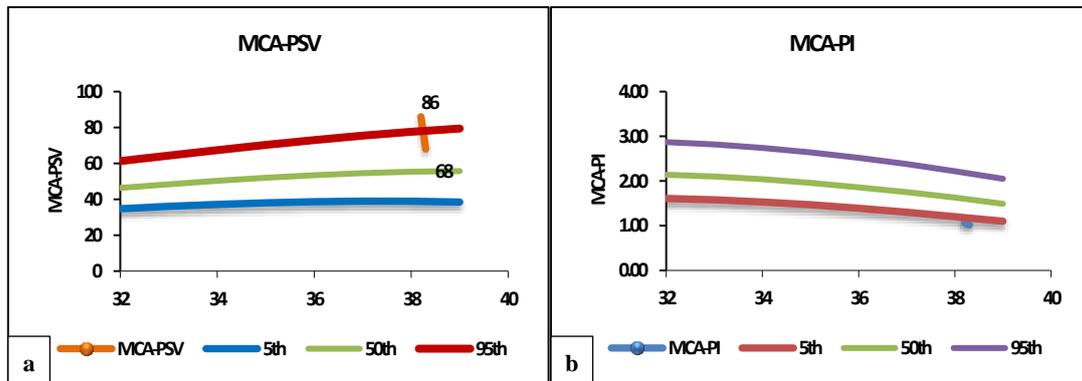
**Table 5: Maternal outcome and correlation with Doppler parameters in late onset IUGR.**

Maternal outcome	Mode of labour (n=23)		P value <sup>1</sup>	Mode of delivery (n=29)			P value <sup>1</sup>
	Induced	Spontaneous		LSCS	NVD	Instrumental	
<b>MCA-PSV</b>							
Normal	9	5	0.340#	12	6	0	0.175#
Abnormal	8	1		7	2	2	
<b>MCA PI</b>							
Normal	9	5	0.340#	12	5	1	1#
Abnormal	8	1		7	3	1	

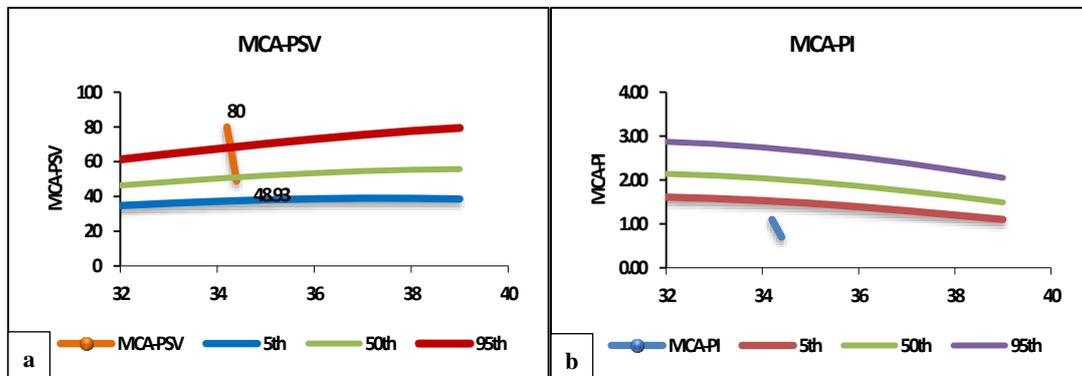
#Fisher exact test.



**Figure 1 (a and b): (Patient no.14) PSV-fall, LSCS/L/NICU/NC/RD/B.W-1680.**



**Figure 2 (a and b): (Patient no.19) PSV-Fall, LSCS/NM/NICU/NC/RD/B.W-1850.**



**Figure 3 (a and b): (Patient no.23) PSV-Fall, NVD/ IUD/B.W-1800.**

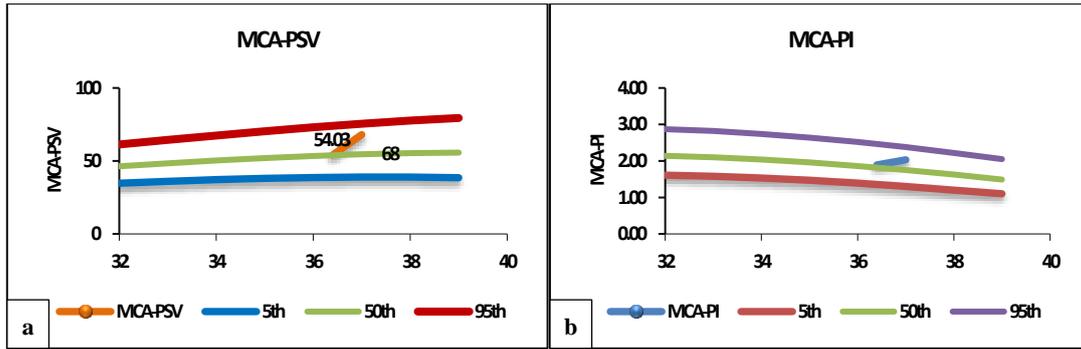


Figure 4 (a and b): (Patient no. 10) LSCS/L/NICU/NC/B.W-1900.

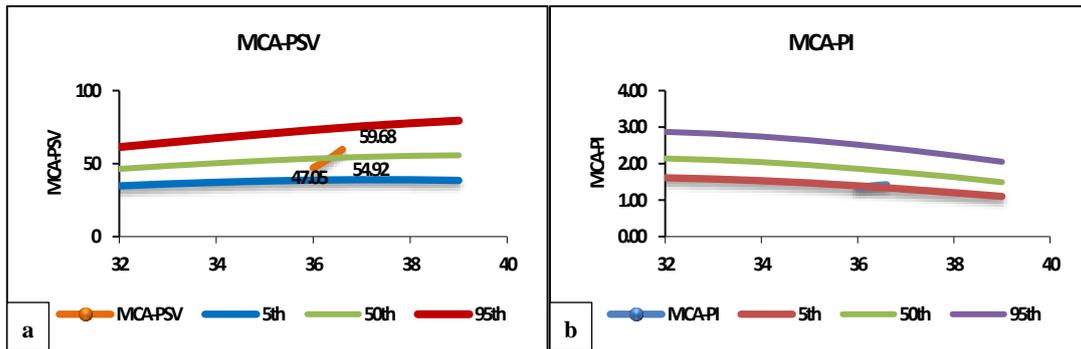


Figure 5 (a and b): (Patient no. 27) LSCS/L/NICU/B.W-1700

LSCS=lower segment caesarean section; NVD=normal vaginal delivery; L=live birth, PM=perinatal mortality (includes: SB=stillbirth; NM=early neonatal mortality; IUD=intrauterine death), NICU=neonatal intensive care unit, NC=neonatal complications (includes hypoglycemia, seizures, sepsis and hypocalcemia).

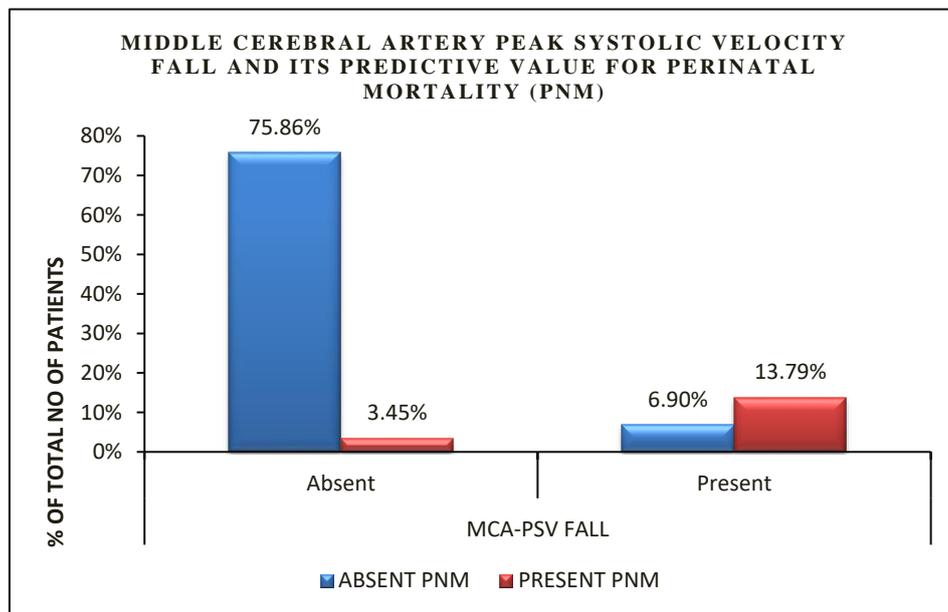


Figure 6: Correlation of MCA peak systolic velocity fall with perinatal mortality.

As shown in Table 2 and Figure 6, out of 6 patients who showed MCA-PSV fall, 4 patients had perinatal mortality

but 2 fetuses with MCA-PSV fall survived. In our study MCA-PSV fall was found strongly associated with

perinatal mortality with p value 0.0003. A good strength of association was there as kappa was 0.664.

In our study NICU admission or stay  $\geq 5$  days, Apgar score  $\leq 7$  at 5 minute and any neonatal complication were taken as perinatal morbidity. Adverse perinatal outcome included both perinatal mortality and morbidity. As shown in Table 3, association of MCA-PSV fall with adverse perinatal outcome was not found significant statistically as p value was  $>0.05$ . Sensitivity and specificity of MCA-PSV fall for predicting perinatal mortality and adverse perinatal outcome has been shown in Table 4. The sensitivity of MCA-PSV fall in predicting the perinatal mortality was 80% with a very high specificity of 91.76% to rule out true negative (Table 4). Maternal outcome and its correlation with Doppler parameters in late onset IUGR had been shown in Table 5. Six patients had elective LSCS so not included in mode of labour.

## DISCUSSION

Pregnancies complicated by IUGR need screening and timely diagnosis in order to prevent unwanted adverse perinatal outcome related to it by intervention at appropriate time. In our study mean age of the patients was 24.97 years and ranged from 19 to 32 years and it is comparable to the study by Gupta et al 2016 showing mean maternal age as  $24.3 \pm 3.57$  and  $25.00 \pm 3.40$  years in their cases and control groups respectively.<sup>6</sup> Mean gestational age at the time of delivery in our study was  $36.65 \pm 1.56$  weeks which was comparable with studies done by Gupta et al (2016) ( $36.10 \pm 0.91$  weeks).<sup>6</sup> We observed pre-eclampsia in 62.06% of patients and oligohydramnios (AFI  $< 5$ ) in 55.17% and 24% patients had both oligohydramnios and pre-eclampsia while Gupta et al (2016) found 70% of women with oligohydramnios in controls and 60% among cases.<sup>6</sup>

In our study on 29 patients of late onset IUGR Doppler examination was done two times in 26 patients and 3 times in 3 patients with  $\geq 32$  weeks period of gestation. While in study by Oros et al (2011) 616 Doppler scans were done on 171 patients with median of 3 times and ranged from 2-9 times.<sup>8</sup> In 72.5% women more than 2 examinations were performed and, in our study,  $>2$  examinations were done in 55% of the cases.

As shown in Figure 1-5 serial Doppler values were plotted on normal reference ranges showing the relation of change in Doppler value with subsequent reading (only 5 patients were shown). They were studied for the longitudinal changes in MCA-PSV and MCA-PI. In 22 patients when MCA-PSV increased there was decrease in MCA-PI which explained that whenever there was decreased resistance in cerebral vessels there was increase in blood flow due to vasodilatation as a marker of fetal adaptive mechanism to hypoxia known as brain sparing effect.<sup>11</sup> But in 7 patients when MCA-PSV increased there was increase in MCA-PI which was not a normal trend in late FGR. This could be due to pseudo normalization

phenomenon due to cerebral oedema which was a grievous finding in such growth restricted fetuses and reflected terminal decompensation due to acidemia following hypoxia.<sup>12</sup> In these patients caesarean section rate was high and babies were delivered early in order to prevent severe insult to the fetus. This pseudo normalization trend had been observed by Kuber et al 2016 also in some growth restricted babies who did not survive.<sup>12</sup> Bano et al (2010) had also stressed on the observation of pseudo normalization and stated that if hypoxia persisted the diastolic flow in MCA returns to the normal level which may not be an indicator of fetal wellbeing but reflected terminal decompensation in the setting of acidemia or brain oedema.<sup>13</sup> Very few studies have been done in India in which such types of longitudinal changes were studied in late onset IUGR in MCA-PI and MCA-PSV.

As shown in Table 3, out of 29 patients who were followed for longitudinal trends there was a fall in MCA-PSV in 6 patients after showing an increasing trend. In 4 patients with MCA-PSV fall there was perinatal mortality as these babies could not be survived. However 2 babies who had MCA-PSV fall but survived were admitted to NICU and had neonatal complications and respiratory distress. MCA-PSV fall was found strongly associated with perinatal mortality with p value 0.0003. A good strength of association was there as kappa was 0.664. The sensitivity of MCA-PSV fall in predicting the perinatal mortality was 80% with a very high specificity of 91.76% to rule out true negative (Table 4). Wladimiroff et al (1986) found that MCA-PSV was more sensitive than MCA-PI for detecting perinatal death in cerebral blood flow Doppler.<sup>14</sup> They also stated that MCA-PSV increased in FGR fetuses due to increase blood flow to the brain. However, factors like vasoconstriction, changes in cardiac contractility or redistribution of cardiac output might contribute to raised MCA-PSV in overstressed fetus prior to death. Rizzo et al 1995 also found that in IUGR patients MCA-PSV increases and remained elevated just prior to fetal demise.<sup>15</sup> Later ACOG practice bulletin (2000) stated that MCA-PSV increased in severely growth restricted fetuses and remained elevated until a few hours prior to fetal death.<sup>16</sup> Mari et al 2007 have shown that MCA-PSV became elevated prior to non-reassuring heart rate tracing like continuous late deceleration or a biophysical profile score  $< 4$  in severe FGR.<sup>8</sup> If MCA-PI was abnormal and MCA-PSV was normal the condition was less severe than in cases where both were abnormal. As FGR condition intensifies MCA-PI started increasing and MCA-PSV started falling, the fetus started to decompensate and death occurred. Thus, MCA-PSV fall appeared to be more sensitive than abnormal MCA-PI for predicting perinatal death as seen in our study. In longitudinal monitoring of MCA-PSV by Gupta et al 2016, there was an initial increase in velocity beyond the 95th percentile followed by a fall prior to intrauterine fetal demise in three fetuses, however the value remained above the upper limit of normal.<sup>6</sup> Specificity of fall of MCA-PSV for predicting fetal death was quite high suggesting that it could be a pre terminal event and termination of pregnancy may be

contemplated when this situation was documented to prevent perinatal mortality. Oczan et al have suggested that MCA-PSV was a good predictor of perinatal mortality in IUGR fetuses.<sup>17</sup>

In our study as shown in Table 5, we found that in maximum number of patients (74%) labour was induced, whereas labour was induced in 66.7% patients in the study by Oros et al 2011.<sup>3</sup> LSCS rate was higher in our study (65.5%) as compared to the studies done by Oros et al 2011 and Nalini et al 2017 who found 53% and 52% caesarean section rate respectively.<sup>3,18</sup>

However mode of labour whether spontaneous or induced was not significantly associated with Doppler parameters studied, this could be due to the reason that most of our clinicians take early decision. Correlation of MCA-PI and MCA-PSV with mode of delivery was also not significant as  $p > 0.05$ .

## CONCLUSION

It is concluded that longitudinal trends of MCA-PSV and MCA-PI provides more useful information than single reading of these parameters. Pseudo-normalization in MCA-PI may be seen with severity in growth restriction but still MCA-PSV is useful as its value will be high followed by a fall predicting imminent death. MCA PSV is a better parameter in predicting perinatal mortality than MCA PI. Thus, MCA-PSV not only complements MCA-PI but it also provides more accurate information than does the MCA-PI alone. It is suggested that MCA-PSV should be used along with MCA-PI for optimizing good fetomaternal outcome.

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