

## **ROLE OF MIDDLE CEREBRAL ARTERY – PEAK SYSTOLIC VELOCITY (MCA-PSV) IN PREDICTING FETOMATERNAL OUTCOME IN LATE ONSET IUGR PREGNANCIES ( $\geq 32$ WEEKS)**

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### **ABSTRACT**

Intrauterine growth restriction (IUGR) is an important clinical issue of pregnancy which is associated with significant compromises in fetus. Currently there is no specific treatment to control IUGR but the time at which pregnancy is terminated is of vital importance as it decreases morbidity and mortality to both the mother and fetus. A prospective observational study was conducted on 53 antenatal patients with fetal growth restriction presenting at  $\geq 32$  weeks in the Department of Obstetrics & Gynecology, Hindu Rao Hospital for one year. The study was aimed to find out if there was any association of Middle cerebral artery – peak systolic velocity (MCA – PSV) with fetomaternal outcome in pregnancies with late onset IUGR ( $\geq 32$  weeks). It was also aimed to compare the performance of Doppler of umbilical and middle cerebral vessels in prediction of perinatal morbidity and mortality in these fetuses. Patient sure of dates or pregnancy confirmed with early first trimester USG with Fetal AC or Effective fetal weight  $< 3^{\text{rd}}$  percentile for that period of gestation by using World Health Organization Fetal Growth Charts or if effective fetal weight / fetal AC was  $< 10^{\text{th}}$  percentile but associated with either UA-PI  $> 95^{\text{th}}$  or CPR  $< 5^{\text{th}}$  percentile for that POG according to available reference value were included in the study. The Doppler parameters (MCA-PSV, UA-PI and MCA-PI) taken on the last scan just prior to delivery were studied for analysis. Maternal and fetal outcome were noted and the data was analysed by using appropriate Statistical tests. Mean gestational age of the patients at the time of enrolment was  $36.51 \pm 1.64$  weeks and it was  $37.0 \pm 1.48$  weeks at delivery. Abnormal Doppler parameters UA-PI  $> 95^{\text{th}}$  percentile, MCA-PI  $< 5^{\text{th}}$  percentile and MCA-PSV  $> 95^{\text{th}}$  percentile were seen in 15.09%, 33.97% and 32.08% respectively. In our study when UA-PI was normal, 28.9% and 33.3% of patients had abnormal MCA-PSV and MCA-PI respectively which indicates that in late onset IUGR, UA may remain normal in comparison to progression of worsening effects in MCA vasodilatation. Perinatal mortality significantly correlated with MCA-PSV with sensitivity and specificity of 80% and 72.02%. Predictive value of MCA – PSV for perinatal mortality and adverse perinatal outcome was also statistically significant (PPV = 23.53% and NPV = 97.22% for perinatal mortality and PPV = 40.54% and NPV = 87.5% for adverse perinatal outcome). MCA PSV is a better parameter in predicting perinatal mortality than UA PI and MCA PI.

**Keywords:** Middle cerebral artery - peak systolic velocity, Intrauterine growth restriction, Fetomaternal outcome in late onset IUGR

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## INTRODUCTION

Intrauterine growth restriction (IUGR) is an important clinical issue of pregnancy which is associated with significantly increased risks of perinatal morbidity and mortality. It is diagnosed when “a fetus fails to reach his/her potential growth” (Bhide *et al.*, 2015 and Cunningham *et al.*, 2018) and affects approximately 10-15 % of pregnant women (Suhag *et al.*, 2013).

The terms intrauterine growth restriction (IUGR) and small for gestational age (SGA) are used for small size babies but they are not synonymous. SGA is usually defined as a neonate with a birth weight for gestational age or abdominal circumference (AC) <10th percentile for a population or customized standard. SGA will include a proportion of babies who are constitutionally small but healthy. At the same time IUGR fetus suffers a pathological condition which is associated with adverse perinatal outcome with significant perinatal morbidity and mortality (Gupta *et al.*, 2016). An IUGR foetus does not need to be small to be growth restricted but it is estimated that the majority of IUGR fetuses are SGA (Bhide *et al.*, 2015). So, these fetuses need to be differentiated from SGA though their clinical differentiation is usually difficult.

Intrauterine growth restriction or fetal growth restriction (FGR) may be classified as early or late depending on the time of diagnosis. Early FGR (<32 weeks) is associated with substantial alterations in placental implantation with elevated hypoxia, which requires cardiovascular adaptation. Late FGR ( $\geq 32$  weeks) presents with slight deficiencies in placentation which leads to mild hypoxia and requires little cardiovascular adaptation, but the degree of tolerance to this hypoxia is low in late onset FGR, in contrast to cases of early onset FGR. The late onset FGR fetus cannot tolerate this low oxygen supply for long time (Mari *et al.*, 2007).

Ultrasound biometry is the most sensitive parameter to predict fetal growth restriction. Most commonly used parameters to diagnose IUGR are effective fetal weight (EFW) and abdominal circumference (AC). EFW is generally calculated by measuring the fetal biometry including femur length, abdominal circumference, bi-parietal diameter and head circumference and using Nomograms (Salomon LJ *et al.*, 2019 and Hadlock *et al.*, 1991). Abdominal Circumference (AC) is related to liver size and tells about fetal glycogen store (Rocha *et al.*, 2017). An estimated fetal weight (EFW) or AC below 10<sup>th</sup> percentile raise concerns of a suboptimal intrauterine growth, however the risk of adverse outcome is proportional to the degree of growth restriction with those below the 3<sup>rd</sup> centile and /or abnormal UA Doppler (Bhide *et al.*, 2015).

In IUGR, umbilical artery Doppler assesses the impedance within the fetoplacental circulation and the pulsatility index and resistance index serve as surrogate markers of placental vascular resistance. When the pulsatility index (PI) of the umbilical artery (UA) is increased, the PI of cerebral arteries decreases due to redistribution of blood to the brain (Oros D *et al.*, 2011). With increased severity the peak systolic velocity (PSV) in MCA increases, as a consequence of increased left cardiac output (Lees *et al.*, 2013).

Blood flow in various vessels has been assessed for the evaluation of FGR for which Umbilical artery Doppler has been studied in detail. Middle cerebral artery is another vessel, but parameter studied has been pulsatility index. Very few studies have used Peak Systolic Velocity in MCA for the evaluation of IUGR fetuses and it is claimed that Middle cerebral artery PSV is a better parameter in predicting perinatal mortality (Gupta *et al.*, 2016 and Mari *et al.*, 2007).

Currently there is no specific treatment to control FGR but the time at which pregnancy is terminated is of vital importance as it decreases morbidity and mortality to both the mother and

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fetus. The present study was aimed to measure UA-PI, MCA – PI and MCA – PSV in late onset IUGR fetuses ( $\geq 32$  weeks) and to find out if there was any association of Middle cerebral artery – peak systolic velocity (MCA – PSV) with fetomaternal outcome in pregnancies with late onset IUGR. It was also aimed to compare the performance of Doppler of these vessels in prediction of perinatal morbidity and mortality in these fetuses.

## **MATERIALS AND METHODS**

This was a prospective observational study conducted on 53 antenatal patients with fetal growth restriction presenting at  $\geq 32$  weeks in the Department of Obstetrics & Gynecology, Hindu Rao Hospital for one year (June 2018 – May 2019). Patient sure of dates or pregnancy confirmed with early first trimester USG with Fetal AC or Effective fetal weight  $< 3^{\text{rd}}$  percentile for that period of gestation (POG) by using World Health Organization Fetal Growth Charts (Kiserud T *et al*, 2017) or if effective fetal weight / fetal AC was  $< 10^{\text{th}}$  percentile but associated with either UA-PI  $> 95^{\text{th}}$  or CPR  $< 5^{\text{th}}$  percentile for that POG according to available reference value (Doppler calculator 2017) were included in the study. It was according to Delphi consensus for late onset growth restricted fetuses (Gordijn *et al*, 2016). Patients with presence or suspicion of congenital anomaly or with multiple pregnancy were excluded from the study. Patients were enrolled after an informed written consent was obtained and the woman was assured of confidentiality. A detailed history was obtained including obstetric history for any past history of FGR or bad obstetric history. A general physical and obstetric examination was performed. By trans-abdominal method using Mind-ray DC 60 Ultrasound machine with trans-abdominal probe of 2-6 MHz, colour Doppler study of umbilical artery was done to obtain systolic to diastolic flow velocity ratio (SD ratio), Resistance index (RI), End diastolic velocity (EDV) and Pulsatility index (PI) Middle cerebral artery was identified and parameters like Peak systolic velocity (PSV), Resistance index (RI) and Pulsatility index (PI) in the absence of fetal breathing and fetal movements. Doppler studies were repeated depending upon the period of gestation and severity of IUGR. A Umbilical Artery pulsatility index, UA-PI of more than  $95^{\text{th}}$  percentile for gestational age according to available reference values were considered abnormal, as also the absent / reversed end-diastolic velocity (ARED) in the UA. The Middle Cerebral Artery waveforms were quantified using the pulsatility index and the peak systolic velocity. The MCA-PSV was considered abnormal if  $> 95^{\text{th}}$  percentile for the gestational age and the MCA-PI was considered abnormal if  $< 5^{\text{th}}$  percentile for the gestational age, according to available Nomograms taken from tables 1 to 4 for the period of gestation. The Doppler parameters taken on the last scan just prior to delivery were studied for analysis. Management of the patients was done as per standard hospital protocol. They were followed till delivery and maternal outcome like need for induction of labour and type of delivery and fetal outcome like birth weight, APGAR score  $< 7$  at 5 minutes, NICU stay along with duration and cause and neonatal death if any was noted. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. The study was approved from the Institutional ethics committee.

## **RESULTS**

Mean gestational age of the patients at the time of enrolment was  $36.51 \pm 1.64$  weeks and it was  $37.0 \pm 1.48$  weeks at delivery. Table 1 shows the distribution of patients according to definition of late onset IUGR (Gordijn SJ *et al*, 2016). 38.09% patients had bad obstetric history and 47.62% had history of FGR in previous pregnancy. Pre-eclampsia was observed in 67.92% of patients

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and oligohydramnios in 52.83% while 9.43% patients had both oligohydramnios and pre-eclampsia. Anaemia was present in 20.75% patients. The distribution of patients of late onset IUGR according to various Doppler parameters in Umbilical and Middle cerebral artery is shown in table 2.

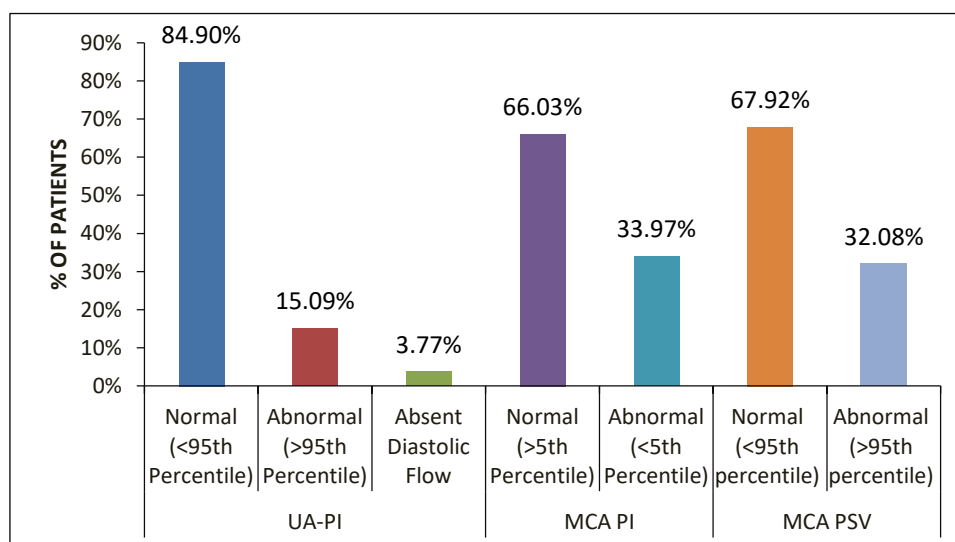
**Table 1: Distribution of patients according to definition of late onset IUGR (Gordijn et al., 2016)**

CRITERION FOR IUGR	NUMBER OF PATIENTS (N=53)	PERCENTAGE (%)
EFW < 3 Percentile	24	45.28%
AC < 3 Percentile	8	15.09 %
EFW < 10 <sup>th</sup> and UA-PI > 95 <sup>th</sup> Percentile or CPR < 5 Percentile	6	11.32%
AC < 10 Percentile and UA-PI >95 Percentile or CPR < 5 Percentile	15	28.30%

**Table 2: Distribution of patients of late onset IUGR according to various Doppler parameters at last scan**

DOPPLER PARAMETERS OF VESSELS	Number of patients	Percentage (%)
<b>UA-PI</b>		
Normal (<95 <sup>th</sup> Percentile)	45	84.90%
Abnormal(>95 <sup>th</sup> Percentile)	8	15.09%
Absent Diastolic Flow	2	3.77%
<b>MCA PI</b>		
Normal ( >5 <sup>th</sup> Percentile)	35	66.03%
Abnormal ( <5 <sup>th</sup> Percentile)	18	33.97%
<b>MCA PSV</b>		
Normal (<95 <sup>th</sup> percentile)	36	67.92%
Abnormal (>95 <sup>th</sup> percentile)	17	32.08%

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

Correlation of Doppler parameters (MCA-PSV, UA-PI and MCA-PI) with various perinatal outcomes and perinatal mortality in late onset IUGR has been shown in table 3 and 4 respectively and fig 2 a, b, c. Adverse perinatal outcome included both perinatal mortality and morbidity. Mean birth weight in our study was  $2081.23 \pm 298.76$  grams which was significantly associated with adverse perinatal outcome with p value 0.001 ( $<0.05$ ) in our study as more complications and mortality was associated with less birth weight.

**Table 3: Perinatal outcome in relation to various Doppler parameters at last scan**

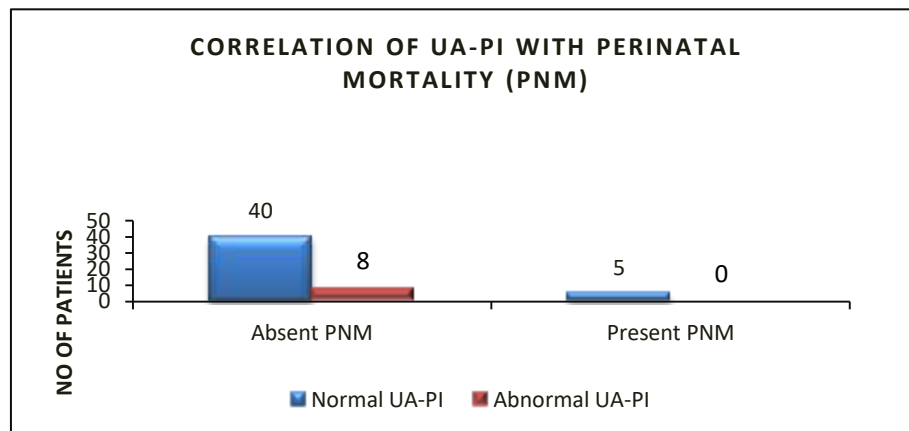
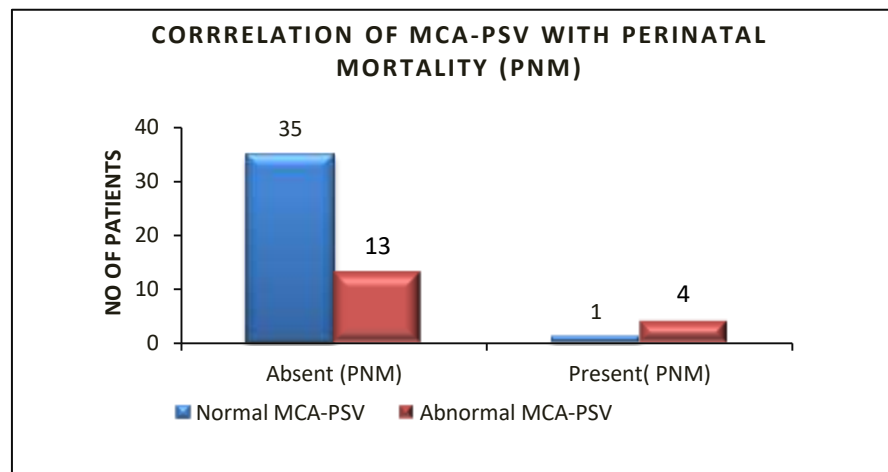
Doppler Parameters	Apgar Score at 5min N=53		Meconium N=53		NICU admission N=53		NICU Duration N=53		Neonatal Complication, N=49	
	>7	≤7	Yes	No	Yes	No	≥5	<5	Yes	No
<b>UA-PI</b>										
Normal N=45	29	16	15	30	27	18	13	32	26	15
Abnormal N=8	2	6	4	4	7	1	3	5	6	2
P-value <sup>1</sup>	0.054		0.436		0.234		0.685		0.696	
<b>MCA-PI</b>										
Normal N=35	22	13	11	24	19	16	7	28	18	15
Abnormal N=18	9	9	8	10	15	3	9	9	14	2
P-value <sup>1</sup>	0.368		0.349		0.068		0.024		0.028	
<b>MCA-PSV</b>										
Normal N=36	25	11	12	24	22	14	10	26	20	15
Abnormal N=17	6	11	7	10	12	5	6	11	12	2
P-value <sup>1</sup>	0.019		0.578		0.502		0.578		0.096	

<sup>1</sup>Fisher exact test

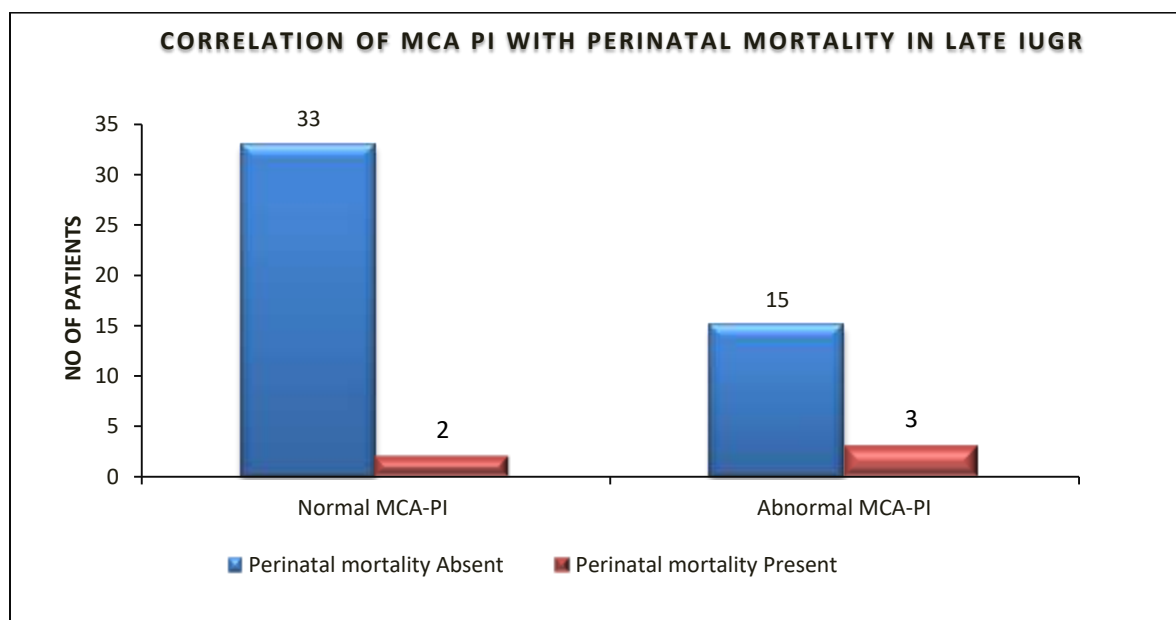
**Table 4: Correlation of Doppler parameters (MCA-PSV, UA-PI AND MCA-PI) with perinatal mortality in late onset IUGR**

		MCA-PSV		Total	P-value <sup>1</sup>
		Normal	Abnormal		
Perinatal mortality	Absent	35	13	48	0.032
	Present	1	4	5	
	Total	36	17	53	
UA-PI					
Perinatal mortality	Absent	40	8	48	1.000
	Present	5	0	5	
	Total	45	8	53	
MCA-PI					
Perinatal mortality	Absent	33	15	48	0.323
	Present	2	3	5	
	Total	35	18	53	

<sup>1</sup> Chi square test



**Figure 2 a, b: Correlation of Doppler parameters (MCA-PSV, UA-PI) with perinatal mortality**



**Figure 2c: Correlation of Doppler parameters (MCA-PI) with perinatal mortality in late onset IUGR**

Table 5 shows the predictive value MCA PSV for perinatal mortality and adverse perinatal outcome. Table 6 shows the correlation of various Doppler parameters with maternal outcomes. Out of 53 patients, 7 had elective LSCS and were not included in mode of labour.

Table 7 shows the correlation of various Doppler parameters in late onset IUGR (UA-PI with MCA-PSV and MCA-PI). MCA-PSV statistically correlated with MCA-PI in late onset IUGR with a p-value 0.045 (<0.05).

**Table 5: Predictive value of middle cerebral artery peak systolic velocity (MCA – PSV) for perinatal mortality and adverse perinatal outcome**

MCA-PSV	Sensitivity	Specificity	PPV	NPV	P-value	Disease Prevalence
Perinatal Mortality	80.00%	72.92%	23.53%	97.22%	0.032	--
Adverse perinatal outcome	88.24%	38.89%	40.54%	87.50%	0.045	32.08%



**Table 6: Maternal outcome observed and their correlation with Doppler parameters in late onset IUGR**

Maternal Outcome	Mode of Labour N=46		P value <sup>1</sup>	Mode of Delivery N=53			P value <sup>1</sup>
	Induced	Spontaneous		LSCS	NVD	Instrumental	
MCA-PSV							
Normal	20	11	0.852	22	13	1	0.050
Abnormal	10	5		9	4	4	
MCA PI							
Normal	19	11	0.966	18	14	3	0.226
Abnormal	11	5		13	3	2	
UA PI							
Normal	24	14	0.694	28	16	1	0.0001
Abnormal	6	2		3	1	4	

<sup>1</sup>Chi square test**Table 7: Correlation of Doppler PARAMETERS (MCA-PSV, MCA-PI AND UA-PI) in patients with late onset IUGR**

UA-PI	MCA-PSV		Total	P-value <sup>1</sup>	Kappa
	Normal	Abnormal			
Normal	32	13	45	0.238	0.144
Abnormal	4	4	8		
Total	36	17	53		
UA-PI	MCA-PI		Total	P-value <sup>1</sup>	Kappa
	Normal	Abnormal			
Normal	30	15	45	0.819	0.028
Abnormal	5	3	8		
Total	35	18	53		
MCA-PI	MCA-PSV		Total	P-value <sup>1</sup>	Kappa
	Normal	Abnormal			
Normal	27	8	35	0.045	0.275
Abnormal	9	9	18		
Total	36	17	53		

<sup>1</sup>Chi square

## DISCUSSION

The period of gestation at which termination of ongoing late onset IUGR pregnancy is done has to be optimized by making balance between the risk of preterm delivery and risks associated with the continuation of IUGR pregnancy. In our study 45.28% of the patients were in the age group of 23-27 years with mean age of  $24.96 \pm 3.54$  years (ranged from 19 to 35 years) which is comparable to the study conducted by Kuber *et al.*, (2016) where 40% of patients were in 21-25 years and 26-30 years age group. Majority of the patients (60.38%) were nulliparous.

As our study focused on late onset IUGR the mean gestational age at the time of enrolment was  $36.51 \pm 1.64$  weeks and ranged from 32.3-39.6 weeks while in a study by Oros *et al.*, (2011) it was  $34.1 \pm 1.6$  weeks. Mean gestational age at the time of delivery in our study was  $37.02 \pm 1.48$



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weeks which is comparable with studies done by Gupta *et al.*, (2016) and Oros *et al.*, (2011) (36.10±0.91 weeks and 38.7±1.7 weeks respectively).

Out of 21 multigravida with late onset IUGR, 47.62% of patients had past history of FGR which is comparable to study by Saad *et al.*, (2014) who found past history of FGR in 34.2% of multigravida. Pre-eclampsia was found in 67.92% patients in our study which is comparable to study by Nalini *et al.*, (2015) and Kuber *et al.*, (2016) who found Pre-eclampsia in 58% and 42% respectively. Oligohydramnios (AFI ≤ 5) was seen in 52.83% cases in our study which is comparable to study by Kuber R *et al.*, (2016) (76%). Anaemia (Hb<11gm%) was seen in 58.49% of patients in our study but it was not comparable to other studies like Nalini *et al.*, (2015) and Kuber *et al.*, (2016) who found anaemia in 24% and 6% patients respectively. Our study included all grades of anaemia including mild also which may be the reason for higher prevalence. Thus pregnancies complicated by IUGR have an association with Pre-eclampsia, oligohydramnios and anaemia.

The Doppler parameters taken on the last scan just prior to delivery were studied for analysis. On analyzing the parameters it was found that abnormal UA-PI (>95<sup>th</sup> centile) was seen in 15.09% patients while 3.77% showed absent end diastolic flow. Abnormal MCA-PI (<5<sup>th</sup> centile) was found in 33.97% patients and abnormal MCA-PSV (>95<sup>th</sup> centile) in 32.08% patients.

Various perinatal outcomes like Apgar score ≤7 at 5 min, meconium and NICU admission along with duration of stay in NICU and neonatal complications (including sepsis, hypoglycemia, hypocalcemia and seizures) were taken as perinatal morbidity and were correlated with various Doppler parameters. MCA-PSV correlated well with Apgar score < 7 at 5 min with a p-value 0.019 (<0.05) which was statistically significant. It is comparable to the study by Nalini *et al.*, (2015) who stated that growth restricted fetuses with abnormal velocimetry were more at poor risk outcome in terms of APGAR score. Also Gupta *et al.*, (2016) found that Apgar score <7 at 5min correlated with abnormal MCA-PSV (p value =0.007). Prolonged NICU stay (>14 days) correlated with abnormal MCA-PSV (p value = 0.00003) statistically in their study. However prolonged NICU stay (>5 days) did not correlate with MCA-PSV (p value = 0.57) in our study but it correlated well with MCA-PI (p-value 0.024). MCA-PI correlated with neonatal complications significantly with a p-value = 0.028 in our study. UA-PI did not correlate statistically with any of the perinatal outcomes.

**Table 8: Comparison of predictive value of MCA-PSV for perinatal mortality with other studies**

STUDY	Sensitivity	specificity	PPV	NPV	P-value
<b>Mari G <i>et al.</i>, (2007)</b>	91%	58%	56%	92%	<0.05
<b>OUR STUDY (2019)</b>	80.00%	72.92%	23.53%	97.22%	0.032

In our study IUD, stillbirth and early neonatal mortality together were taken as perinatal mortality. MCA-PSV was significantly associated with perinatal mortality (0.032) however correlation of UA-PI and MCA-PI was not significantly associated with perinatal mortality in late onset IUGR patients. (P-value = 1.000 and p-value= 0.323 respectively)

Predictive value of MCA PSV for perinatal mortality was statistically significant (p value = 0.032) in our study. Oczan *et al.*, (1998) have also found that MCA-PSV is a good predictor of

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perinatal mortality in IUGR fetuses. Comparison of predictive value of MCA-PSV for perinatal mortality with other studies has been shown in table 8.

As shown in table 5 the sensitivity of MCA-PSV in predicting the adverse perinatal outcome was 88.24% with a specificity of 38.89%. Association of MCA-PSV with adverse perinatal outcome was found significant statistically as p-value was 0.045 and thus it has a good ability to predict the adverse perinatal outcome. Comparison of predictive value of MCA-PSV for adverse perinatal outcome with other studies has been shown in table number 9.

**Table 9: Comparison of predictive value of MCA-PSV for adverse perinatal outcome with other studies**

STUDY	Sensitivity	Specificity	PPV	NPV	P-value
Gupta S <i>et al.</i> , (2016)	90.91%	100%	100%	90%	0.05
Our study (2019)	88.24%	38.89%	40.54%	87.50%	0.045

In our study as shown in table 6, labour was induced in maximum number of patients (56.60%), whereas in the study by Saad *et al.*, (2014) induction was done in 53.3% of patients of late onset FGR and 66.7% patients in the study by Oros *et al.*, (2011). Though induction of labour was done in majority of patients but mode of labour whether spontaneous or induced was not significantly associated with Doppler parameters studied which shows that UA-PI is not relevant in making decision for induction in late onset IUGR.

LSCS rate was high 58.49% in our study which is comparable to the studies done by Oros *et al.*, (2011) and Nalini *et al.*, (2015) who found 53% and 52% caesarean section rate respectively. UA-PI was significant in relation to mode of delivery with p-value <0.0001, however the correlation of MCA-PSV Doppler with mode of delivery was borderline significant. Most of our clinicians take decision on umbilical artery Doppler and not on MCA Doppler.

As shown in table 7 our study indicates that UA-PI did not statistically correlated with MCA-PSV and MCA-PI in late onset IUGR as p-value were 0.238 and 0.819 respectively (>0.05). However, correlation of MCA-PI with MCA-PSV Doppler was found statistically significant in late onset IUGR patients (p-value <0.05).

In our study when UA-PI was normal, 28.9% and 33.3% of patients had abnormal MCA-PSV and MCA-PI respectively which indicates that in late onset IUGR, UA may remain normal in comparison to progression of worsening effects in MCA vasodilatation. Oros *et al.*, (2011) have also concluded the same and have discouraged the use of UA as a single parameter for late onset SGA fetus surveillance.

Mari *et al.*, (2007) concluded that the MCA-PI along with the UA-PI, should be considered the gold standard for the assessment of IUGR fetuses and suggested that not only does the MCA-PSV complement MCA-PI but it also provides more accurate information than does the MCA-PI alone. They further said that in IUGR fetuses with an abnormal MCA-PI and a normal MCA-PSV, the condition of IUGR was less severe compared to cases where MCA-PI and MCA-PSV both are abnormal. They also found that MCA-PSV increases along with increase in the severity of IUGR condition and becomes abnormal. Also Nalini *et al.*, (2016) stated that IUGR with abnormal flows in MCA leads to high morbidity and mortality. Gupta *et al.*, (2016) also suggested that MCA-PSV should be used along with MCA-PI for optimizing good fetomaternal outcome.

## CONCLUSIONS

Intrauterine growth restriction is a very complex and serious issue for obstetrician not only in India but worldwide as its diagnosis and management is always a challenge. MCA PSV is a better parameter in predicting perinatal mortality than UA PI and MCA PI. Pseudo-normalization in MCA-PI may be seen with severity in growth restriction but still MCA-PSV is better as its value correlates not only with adverse perinatal outcome (p-value=0.045) but has a good predictive value for adverse perinatal outcome.

## LIMITATIONS

This study was conducted in a single center which might not be representative of whole population. Abnormal UA Doppler is an indication for delivery for ethical reasons so the temporal relationship between the parameters studied may be biased. Venous Doppler and Aortic isthmus study not performed which may have provided some more information.

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