

## **Fetal Growth Restriction and Doppler Waveform**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. Author NS designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Authors JR and BMS managed the analyses of the study. Author JR managed the literature searches. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Background:** Fetal growth restriction (FGR) is defined as the estimated fetal weight less than the 10<sup>th</sup> percentile for that gestational age on ultrasound study. There is no proven cure; management is reliant on a structured antenatal surveillance programme. Recent advances in ultrasound and Doppler have elucidated several mechanisms of growth restriction. Prediction of intrauterine hypoxia and acidemia can be done by Doppler study of fetal cardiovascular system.

**Objectives:** To analyse the uteroplacental and fetoplacental blood flow using Doppler ultrasound in growth-restricted fetuses with reference to flow velocity and waveform indices.

**Materials and Methods:** This prospective study employed Doppler ultrasound examination of the fetal cardiovascular system after 28 weeks of gestation in 32 singleton pregnancies with fetal growth restriction.

**Results:** In the present study preeclampsia and maternal anaemia were found to be the most important cause of fetal growth restriction. Abnormal Doppler indices in umbilical and middles

cerebral artery statistically correlated with lower birth weights, higher rate of caesarean delivery, oligohydramnios, low Apgar scores, perinatal death and higher admission to neonatal intensive care unit. Reduced end diastolic flow or complete absence of it in the umbilical artery is associated with poor perinatal outcome. Cerebroplacental Ratio (pulsatility index of middle cerebral artery/pulsatility index of umbilical artery) less than 1 is a very sensitive and specific sign of fetal compromise.

**Conclusion:** Abnormal Doppler waveforms within the umbilical and middle cerebral arteries are indicative of redistribution of cerebral blood flow in fetal hypoxia. If there is reduced or low blood flow during diastole in umbilical arteries, the fetal perfusion becomes intermittent and fetal hypoxia develops. The blood flow redistributes to vital organs like brain and kidneys and the pulsatility index of middle cerebral artery falls in the fetus. The plausible explanation of it is, sympathetic activation in a hypoxemic fetus leading to increased cerebral perfusion. The ductus venosus flow gets reduced and reversed along with continued hypoxia.

**Keywords:** Fetal growth restriction; doppler; middle cerebral artery; ultrasonography and umbilical artery.

## ABBREVIATIONS

*FGR* : Fetal Growth Restriction  
*CPR* : Cerebroplacental Ratio  
*NICU* : Neonatal Intensive Care Unit  
*MCA* : Middle Cerebral Artery  
*PI* : Pulsatility Index  
*LSCS* : Lower Segment Caesarean Section  
*CTG* : Cardiotocogram  
*EDV* : End Diastolic Volume  
*CRL* : Crown Rump Length  
*UNICEF* : United Nations Children's Fund

## 1. BACKGROUND

Fetal Growth Restriction (FGR) is defined by the international fetal medicine experts with consensus on single best parameter either Estimated Fetal Weight/Abdominal Circumference less than 3rd percentile for that gestational age, or absence of umbilical artery end diastolic flow [1]. FGR is the result of numerous pathologies that reduce fetal cell size and when these pathologies are very early and severe occurring before 20<sup>th</sup> week, there is also a reduction in fetal cell number, which is known as hypoplasia (early onset FGR). When these pathologies are late, the cell number remains normal but the cell size becomes small resulting in small babies (late onset FGR)[2].

Thus, there are two types of fetal growth restriction- the early and the late onset FGR [2]. In the first type, there is suboptimal number of fetal cells, and there is intrinsic or symmetrical fetal growth restriction. Intrinsic FGR arises from fetal conditions such as infections or chromosomal abnormalities. These fetuses grow

slowly because their growth potential has been permanently affected by a severe change in the first trimester and tend to grow in a low percentile in the gravidogram. Medical interventions like NO donors to improve the fetoplacental flow have little or no effect. Furthermore, the fetal sympathetic system is immature before 20<sup>th</sup> week and is unable to employ any adaptive mechanisms.

Usually extrinsic causes are responsible for the late onset FGR and the growth failure is due to external factors such as, placental insufficiency, maternal malnutrition, preeclampsia, chronic maternal medical diseases. The fetal sympathetic system gets mature and various adaptive mechanisms and redistribution of nutrients are employed at the fetomaternal interphase. Subsequently a sonologically evident asymmetrical FGR develops.

According to a recent UNICEF survey, the occurrence of FGR in developing countries is about 25-30%. Current challenges in the clinical management of FGR include accurate diagnosis of truly growth-restricted fetuses, selection of appropriate fetomaternal surveillance markers and optimising the time of delivery. Fetal gestational age has to be assessed precisely because of the risk of adding the problem of prematurity to growth restriction. If a decision of a premature fetus delivery is made because of restricted growth, steroids should be given to prevent acute respiratory distress syndrome of lungs and MgSO<sub>4</sub> for neuroprotection.

Trials have shown Doppler interrogation of umbilical artery and middle cerebral artery remains the most useful and practical tool in

identifying fetuses as the risk of the adverse perinatal outcome, identifying around 88% of all adverse outcomes [3,4].

## 2. MATERIALS AND METHODS

This prospective study involved Doppler ultrasound examination of the umbilical arteries at 28<sup>th</sup> week of gestation in women with singleton pregnancies attending a routine scan. This study was approved by the ethical committee and the research board. All women with no major fetal anomaly were offered the option of uteroplacental and fetoplacental artery Doppler evaluation. Written consent was obtained in all the cases. A first-trimester scan was done to measure the Crown Rump Length (CRL) to study the pregnancy in all cases.

The study was carried out on 697 pregnancies in the Department of Radiology and Department of Obstetrics and Gynecology at Saveetha Medical College and Hospital, Chennai, India between 1 April 2015 and 31 December 2016 after getting written informed consent from participants in the local language. Multiple Pregnancies and pregnancies with congenital anomalies were excluded. Detailed maternal factors like age,

gestational age, parity, pre-pregnancy body mass index, previous low birth weight, haemoglobin levels, chronic hypertension, gestational diabetes and previous preeclampsia were recorded. Placental problems like infarcts, retro placental calcifications, small placenta, and premature separation were noted. The ultrasound machines used for the study were procured from PHILIPS HD11XE (Acuson, Mountain View, CA, USA); GE LOGICS7 Expert; Siemens Sonoline Acuson X150 (Siemens).

Pulsatility index (PI) was considered rather than resistivity index because PI describes the shape of the velocity waveform much better as it includes the area below the curve into the formula. Presence or absence of an early diastolic notch was recorded. 125 Hz high pass filter was used to eliminate the signals from slowly moving tissues. The curved transducer (3.5-or 5-MHz) had spatial peak temporal average intensities <100 mW/cm<sup>2</sup>. Recordings for measurements were obtained in the absence of fetal breathing movements and fetal heart rate between 120 -160 beats per minute. The angle between the ultrasound beam and the direction of blood flow was always less than 30°.

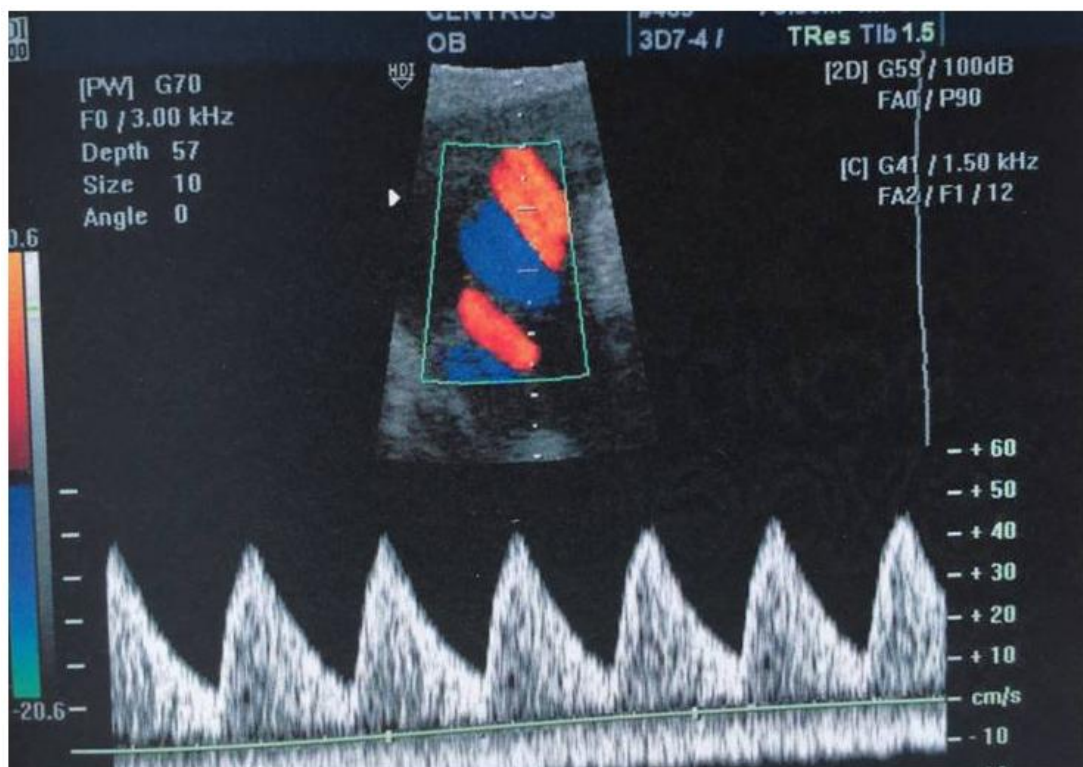
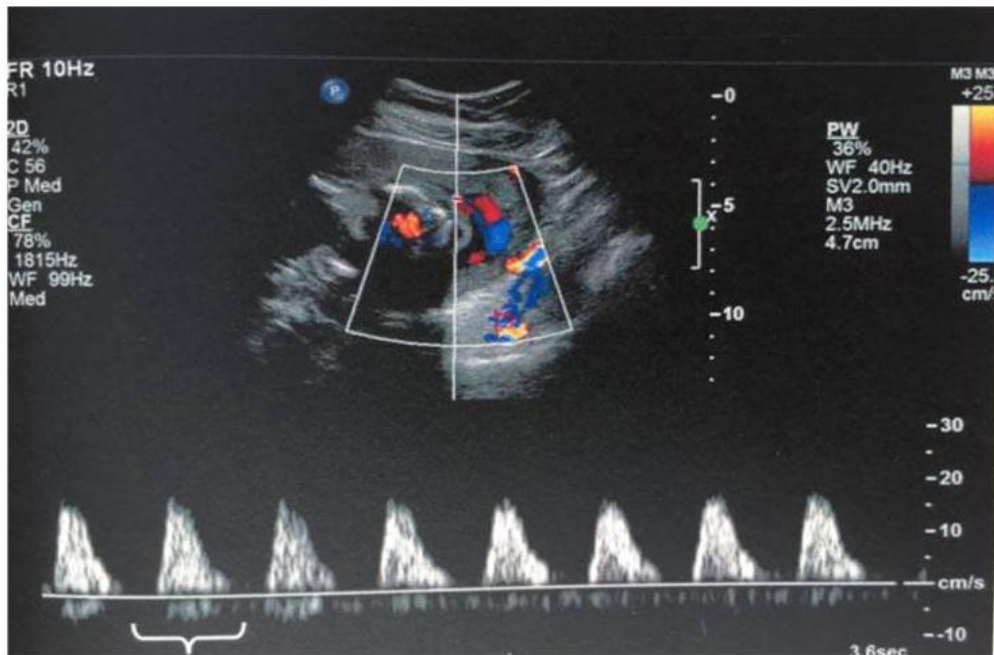
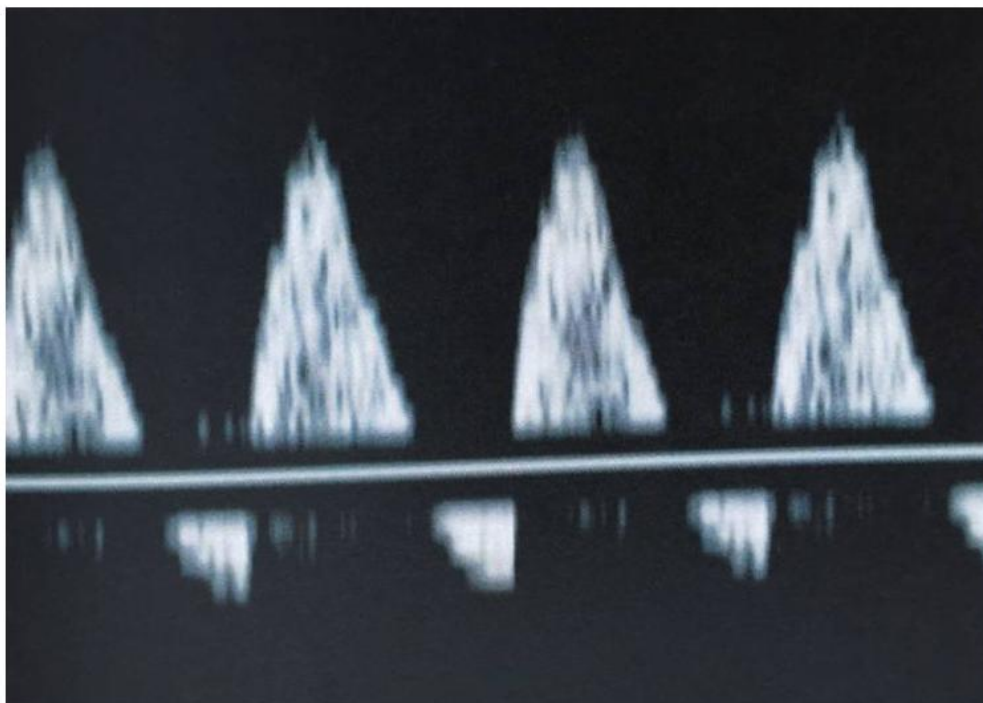


Fig. 1 (a). Normal blood flow in umbilical artery



**Fig. 1(b).** Doppler showing absent end diastolic flow in the Umbilical artery: Absent end diastolic flow (AEDF): RI = 1



**Fig. 1(c).** Reversed Diastolic flow in the umbilical artery

FGR was defined as the fetal weight below the expected weight in the customized population fetal growth charts [5]. The patients of FGR were followed up by weekly serial scans after 28 weeks and Doppler velocimetry studies of umbilical

artery and middle cerebral arteries were done to identify the severity of uteroplacental insufficiency and brain sparing effect. Umbilical Artery Doppler measurements were obtained in the free loop. Fig. 1 depicts the umbilical artery

PI. The normal flow is high velocity and low pulsatility Index {Fig. 1(a)}. With increasing fetoplacental insufficiency, the diastolic flow gets reduced or absent {Fig. 1 (b)}. The blood starts

flowing back from the fetus to the placenta if the fetoplacental perfusion is further compromised. This is called as reversed diastolic flow in umbilical artery {Fig. 1(c)}.

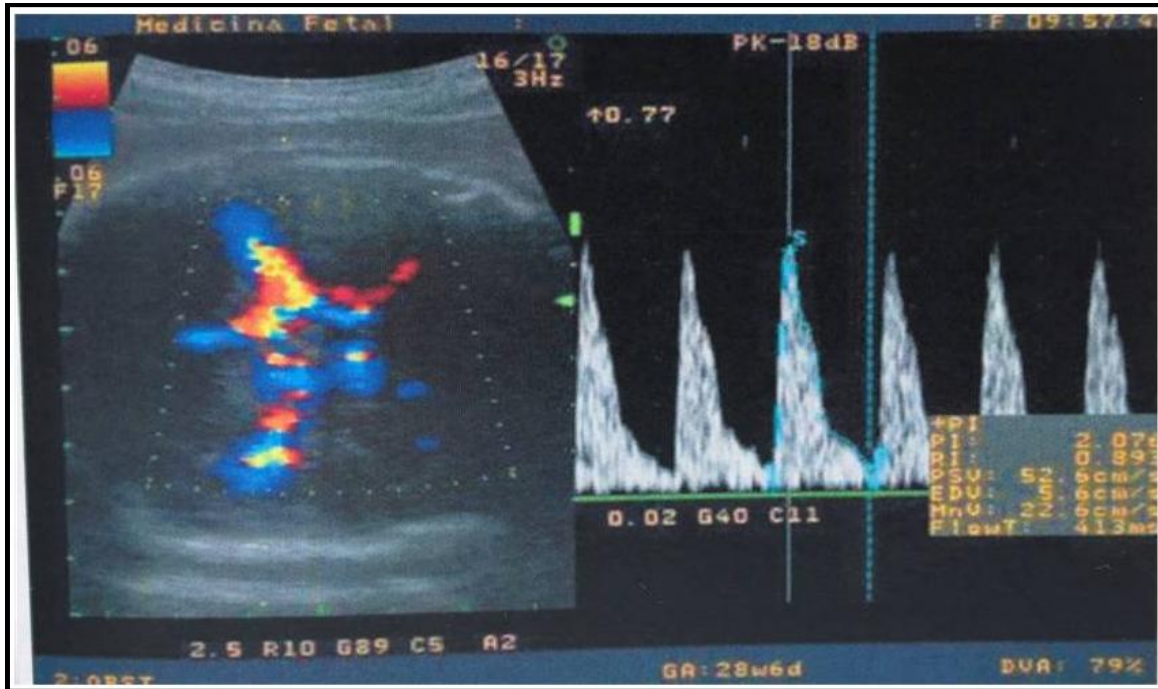


Fig. 2(a). Doppler velocimetry of the middle cerebral artery visualized from the circle of Willis and insonated immediately after its origin from the internal carotid artery

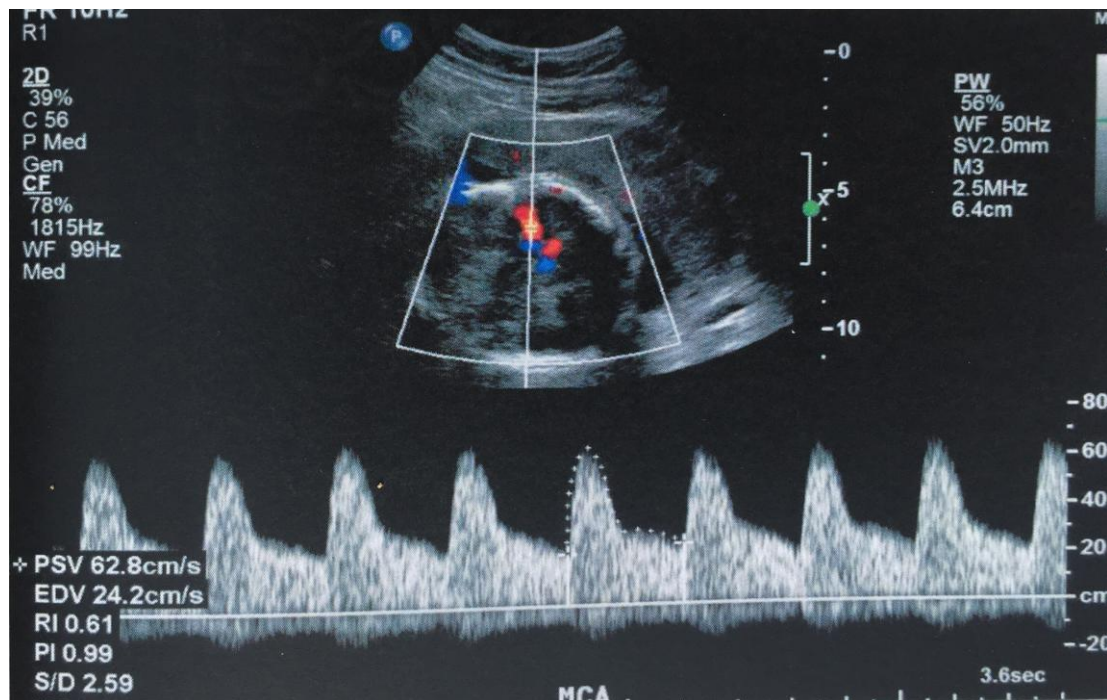


Fig. 2(b). Brain sparing effect in middle cerebral artery: An adaptive mechanism to the suboptimal intrauterine environment, in IUGR pregnancies

The fetal Middle Cerebral Artery (MCA) Doppler evaluation was formulated by obtaining a fetal axial section including fetal thalamic nuclei on the scan, if there is absence or reduced flow in the umbilical artery. Colour flow mapping was used to identify the circle of Willis. The measurement was made on the proximal third of the MCA where it is close to its origin in the internal carotid artery. Fig. 2(a) and 2 (b) show the normal and decreased PI of MCA. Ductus Venosus was seen by midsagittal plane of the fetal trunk. Colour flow mapping was used to identify the alignment where the high velocity of the vessel can be seen at its narrow entrance. All Doppler waveforms were calculated only after obtaining three consecutive waveforms. Statistical analysis was done using MEDCALC.

### 3. RESULTS

Doppler examination was done in 750 pregnancies. Satisfactory waveforms were obtained in 743 pregnancies (99%). During the study period, a follow up was available for a total of 697 pregnancies. Out of total 697 pregnancies, a total of 32 (4.59%) pregnancies resulted in FGR neonates. There were no intrauterine deaths. There was a significant association of maternal age >34 years with FGR (Odds Ratio 241.5192, Confidence interval 72.0261 to 809.8671, Z statistic 8.889, p-value

<0.0001). Out of 32 cases, 7 were early onset (<32 weeks), and 25 were late onset (>32 weeks). Thirteen cases of FGR had pregnancy-induced hypertension. In twelve cases there was severe or very severe anaemia. In 4 cases there were placenta praevia. In two cases there was velamentous cord insertion. Out of 32 fetal growth restricted newborns, 31 survived beyond four weeks of life. Table 1 summarises the maternal history variables associated with the FGR. In 2 neonates (6.25%) no maternal cause of FGR could be identified.

Colour Doppler Findings were abnormal in 29/32 FGR. All 3 pregnant women with normal Doppler study were induced for vaginal labor. One patient delivered vaginally and two had Lower Segment Caesarean Section (LSCS) for non-reassuring fetal heart on Cardio Toco Gram (CTG). Table 2 shows the average birth weight and number of days of Neonatal ICU admission for normal and abnormal Doppler study of neonates.

It was seen that, gestational age rather than weight was a predictor of neonatal mortality, as all FGR babies beyond 34 weeks had no neonatal mortality. Table 3 brings up the abnormal colour Doppler findings in FGR fetuses (29/32). All these newborns were delivered by Caesarean Section.

**Table 1. Maternal history variables associated with the intrauterine growth Restriction**

Factors	No of Cases
Preeclampsia	13/32
Maternal Anemia (severe and very severe)	12/32
Gestational Diabetes / Overt Diabetes	9/32
Maternal Age >34	19/32
Placenta Praevia	4/32
Velamentous Cord Insertion	2/32
No Maternal Cause Identified	2/32

**Table 2. The average birth weight and number of days of neonatal ICU admission for normal and abnormal Doppler study of neonates**

Doppler study	No. of newborns	Average birth weight	Average days in NICU
Normal Umbilical artery and normal Middle cerebral artery	3/32(9.38%)	1800 gms	38
Abnormal Umbilical artery and/or normal Middle cerebral artery	29/32(90.62%)	1760 gms	59

**Table 3. Abnormal color Doppler findings in IUGR fetuses**

<b>Doppler derangement</b>	<b>No. of cases</b>	<b>Percentage</b>	<b>Average NICU admission days</b>
Decreased End diastolic flow in the Umbilical Artery with normal middle cerebral artery (CPR>1)	14/32	43.75%	46
Decreased End Diastolic flow in the Umbilical Artery with abnormal Middle Cerebral Artery (CPR<1)	6/32	18.75%	58
Absent/reversed End diastolic flow in the Umbilical Artery with Normal Middle Cerebral Artery (CPR >1)	1/32	3.13%	67
Absent/reversed End diastolic flow in the Umbilical Artery with Abnormal Middle Cerebral Artery (CPR <1)	7/32	21.87%	66
CPR Ratio <1 with Decreased Flow in Ductus Venosus	1/32 (Early neonatal Death)	3.13%	Died on Day 4 Necrotizing enterocolitis)

#### 4. DISCUSSION

In the present study there were 32 FGR cases with high abnormal umbilical PI in 29/32 pregnancies. Abnormal umbilical artery Doppler is characterized by reduced or absent forward flow in diastole and increased resistance (6). Absent end diastolic flow is noted when 75% of the placental bed has been obliterated [7]. Reversed end diastolic flow is an end stage finding when the fetus is severely compromised and a decision to deliver the fetus has to be made.

Other indications of fetal Doppler are fetal anaemia, fetal infections, feto-maternal haemorrhage, preeclampsia, fetal cardiac failure and pre and post-fetal exchange transfusion in cases of red cell alloimmunisation [8]. The Doppler is done bi-weekly from 26<sup>th</sup> week onwards. Abnormal umbilical artery Doppler is an indication of further workup of the degree of uteroplacental insufficiency; that is the fetal MCA Doppler assessment [9,10]. If the PI of middle cerebral artery is reduced, then the ductus venosus and umbilical vein flow should also be assessed [11,12].

The fetal head sparing theory has been proposed in asymmetrical intra-uterine growth restriction, where the difference between normal head circumference and decreased abdominal

circumference is attributed to the fetus's ability to preferentially supply the cerebral, coronary, and adrenal and splenic circulations. In a situation of chronic fetal hypoxemia, the fetus redistributes its cardiac output to maximize the oxygen supply to the brain by vasodilatation of the cerebral arteries and thus there is reduced PI of the middle cerebral artery. This ensures a decreased left ventricular after load. Few recent studies have also emphasized about the role of aortic isthmus Doppler study when umbilical artery pulsatility index is high as this vessel directly measures the cardiac output in a compromised fetus. Aortic isthmus flow index is found to be increased in the growth-restricted fetuses. Absolute end-diastolic (EDV) and mean velocities are usually decreased in the FGR fetuses [13,14,15]. Diagnosis of FGR is a challenge in routine obstetric practice. Vigilant surveillance, antenatal treatment with steroids to enhance maturity and optimizing the time of delivery can prevent fetal and neonatal complications [16].

#### 5. CONCLUSION

Doppler waveform analysis is a useful biophysical marker. The study concludes that umbilical artery Doppler identifies a subset of FGR with a compromised fetoplacental circulation. When umbilical artery circulation is abnormal, fetal middle cerebral artery study is

done. It is a serious situation when the fetus is shunting its flow to vital organs like the brain. The fetus manifests as decreased pulsatility index of the middle cerebral artery and alteration of cerebroplacental ratio. If the middle cerebral pulsatility index is low it becomes an indication to assess the ductus venosus and umbilical vein flow.

The Doppler study of FGR in pregnancy can be useful in identifying fetus that needs increased surveillance to decide the time of delivery [16,17,18]. There is an emerging role of ductus venosus and aortic isthmus Doppler study to identify the severely hypoxic fetuses. Strict criteria should be used when performing advanced fetal Doppler. The Doppler findings need to be correlated in context of clinical fetal growth assessment [19,20,21].

## DISCLAIMER

This particular research has some limitations. Authors declared that *“There were 32 IUGR babies in 697 pregnancies. The sample size is small. This is also further classified. There is no control group. For any statistical test to have meaningful implications the sample size should be reasonable. We did approach a statistician but it was concluded that it was not possible to make 2X2 tables in the present study”*. Readers’ attention is requested regarding this limitation. A detailed discussion is available in the peer review history files.

## CONSENT

As per international standard or university standard, patient’s written consent has been collected and preserved by the authors.

## ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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