

**Original article:**

## **Importance of cerebroplacental ratio in prediction of adverse perinatal outcome in IUGR fetuses of western Maharashtra population**

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### **ABSTRACT**

#### **Objectives:**

1. To evaluate the distribution of Doppler pulsatility index (PI) measurements of the umbilical and middle cerebral arteries & Cerebroplacental ratio values in western Maharashtra population coming to tertiary care centre, Fetal Medicine unit, SKNMC, Pune.
2. To evaluate the distribution of these Doppler values with neonatal outcome in IUGR fetuses.
3. To evaluate the distribution of these Doppler values with perinatal morbidity.

**Materials and methods** - A prospective observational study was performed at Fetal Medicine Unit, SKNMC, Pune, from September 2014 to August 2017. Total 4579 women were screened at routine antenatal visit during this period, out of which 248 were selected.

**Results** - Abnormal CPR values at 28 - 32 weeks, 32 - 37 weeks & 37 - 42 weeks (Figure no. 2 - 8) has shown clear cut increased in cesarean section rate, NICU admission and duration of stay in NICU, Intrauterine deaths, low birth weight. We have categorically identified that CPR values < 5<sup>th</sup> centile and > 95<sup>th</sup> centile clearly increases perinatal morbidity & mortality. We have seen that there is substantial increase in intrauterine and neonatal deaths at < 5<sup>th</sup> centile.

**Conclusion** – Abnormal CPR in IUGR cases was independently associated with increased need for operative delivery for presumed fetal compromise and admission to the NICU. the rate of operative delivery for presumed fetal compromise was higher in AGA fetuses with low CPR. Our results suggest that the categorization of the at-risk fetus according to size alone is inadequate. We have labelled IUGR cases as per Delphi consensus.

### **INTRODUCTION –**

Intrauterine growth restriction (IUGR) is associated with adverse perinatal outcomes. The use of Doppler velocimetry has been shown to reliably predict these adverse outcomes. (1) For the majority of pregnancies, the placenta provides adequate metabolic and oxygen supply to the fetus throughout the birth without any detrimental effects on growth or wellbeing. However, when placental function is suboptimal impaired fetal growth can supervene. Fetal hypoxia is one of the major causes of high perinatal morbidity and mortality rates. (2,3) Doppler investigation of the fetal circulation can give important clues to fetal well-being in a number of fetal conditions. The unique arrangement of the fetal circulation allows afterload to affect ventricles individually. The future fetal growth velocity is in turn reflected with various dopplers and their proportions. (4)

The fetal cerebroplacental ratio (CPR) is the ratio of the fetal middle cerebral artery (MCA) pulsatility index (PI) to umbilical artery (UA) PI. It is believed to be a proxy for suboptimal fetal growth given it quantifies both suboptimal placental function and subsequent fetal circulatory adaptations. CPR is emerging as an important predictor of adverse pregnancy outcome, and this has implications for the assessment of well-being in fetuses diagnosed for fetal growth restriction (FGR).

The CPR represents the interaction of alterations in blood flow to the brain. MCA doppler manifest by increased diastolic flow and PI is a result of cerebrovascular dilatation resulting from hypoxia. Umbilical artery doppler the increased placental resistance, resulting in decreased diastolic flow. (5)

These are the two variables whose parameters are difficult to compare at a single glance, hence we use the ratio. Most of the previous studies on the efficacy of the CPR used categorical cutoff thresholds of the Ratio which were not co-relating with the outcomes. Baschat and Gembruch developed a gestational age-based nomogram for the CPR. (4) Many articles with gestational age specific levels in prediction of IUGR has come with western population data. There is limited study in Indian population mainly in western India. it is our sincere approach to know about the facts.

#### **Objective-**

1. The objective of this study was to determine the effect of using the gestational age-specific reference levels of the CPR on the prediction of adverse perinatal outcomes compared with the use of categorical thresholds in IUGR fetuses.
2. To evaluate the distribution of Doppler pulsatility index (PI) measurements of the umbilical and middle cerebral arteries & Cerebroplacental ratio values in western Maharashtra population coming to tertiary care centre, Fetal Medicine unit, SKNMC, Pune.
3. To evaluate the distribution of these Doppler values with neonatal outcome in IUGR fetuses.
4. To evaluate the distribution of these Doppler values with perinatal morbidity.

#### **MATERIALS AND METHODS -**

A prospective Observational study was performed at Fetal Medicine Unit, SKNMC, Pune, from September 2014 to August 2017. Total 4579 women were screened at routine antenatal visit during this period, out of which 248 were selected.

Inclusion criteria - 1) Pregnant women more than or equal to 28 weeks of gestation with diagnosed IUGR by Delphi Consensus criteria on first visit to the department.

- 2) Women who are willing to perform the doppler study (written informed consent taken).

Exclusion criteria - 1) Pregnant women who are less than 28 weeks of gestation.

- 2) Multifetal pregnancies.
- 3) Pregnancies with abnormal fetal anatomy
- 4) Previously diagnosed cases of IUGR.

The criteria for IUGR is as per Delphi consensus. For early FGR (< 32 weeks), three solitary parameters (abdominal circumference (AC) < 3<sup>rd</sup> centile, estimated fetal weight (EFW) < 3<sup>rd</sup> centile and absent end-diastolic flow in the umbilical artery (UA)) and four contributory parameters (AC or EFW < 10<sup>th</sup> centile combined with a pulsatility index (PI) > 95<sup>th</sup> centile in either the UA or uterine artery).

For late FGR ( $\geq$  32 weeks), two solitary parameters (AC or EFW < 3<sup>rd</sup> centile) and four contributory parameters (EFW or AC < 10<sup>th</sup> centile, AC or EFW crossing centiles by > two quartiles on growth charts and cerebroplacental ratio < 5<sup>th</sup> centile or UA-PI > 95<sup>th</sup> centile)

This visit included recording of maternal characteristics and medical history, and estimation of fetal size from transabdominal ultrasound measurement of biparietal diameter fetal head circumference, abdominal circumference and femur length. Determination of gestational age was done from menstrual history or measurement of the fetal crown-rump length at 11 weeks - 13 weeks 6 days gestation or the fetal head circumference at 19–24 weeks (6).

UA and MCA were visualised by transabdominal colour doppler. Pulsed-wave Doppler was then used to assess impedance to flow; when three similar waveforms were obtained consecutively the PI was measured (7) Doppler studies were performed using Seimens Acuson X300 Ultrasound machine by single Fetal medicine specialist using 5-MHz sector transducers with spatial peak temporal average intensities below 50 mW/cm<sup>2</sup> and the high-pass filter at 50–100 Hz. The said fetal medicine specialist had accreditation to FMF (Fetal Medicine Foundation).

Umbilical artery pulsatility index is measured at its midportion (4). The middle cerebral artery is visualized in a transverse axial view of the fetal head at a slightly caudal plane than one used for biparietal diameter measurements which were made from the middle section of middle cerebral artery.

For measurements of the middle cerebral artery an axial view of the fetal head was obtained at the level of the cerebral peduncles at base of skull, within 2 mm of internal carotid artery origin, then the color Doppler was used to visualize the circle of Willis, and the Doppler sample volume was placed within 1 cm of the origin of the middle cerebral artery that was easily identified as a major branch running anterolateral from the circle of Willis toward the lateral edge of the orbit. The Doppler signals were recorded with a 5 MHz curved array duplex transducer. The sample volume size was 2 mm. Angle of insonation kept as close to 0° as possible. Waveforms of good quality were collected and analyzed in the absence of fetal breathing movements. Waveform analysis was performed by measuring in the frozen display the maximum and minimum values of the velocity waveforms with the electronic calipers of the instrument (8).

All images taken during this study were stored at PACS (Picture archiving and data system) electronic database at Fetal Medicine department, SKNMC. When at least five consecutive uniform flow velocity waveforms with a high signal-to-noise ratio were obtained during periods of fetal rest and apnea the image was frozen and the waveforms were quantified using the PI.

An abnormal CPR was defined as a CPR of more than 95<sup>th</sup> percentile or a CPR below the 5<sup>th</sup> percentile for gestational age on the basis of the nomogram by Baschat and Gembruch. (2)

Maternal parameters studied were weeks of gestation, mode of delivery (vaginal or Cesarean section), complications during pregnancy ( oligohydramnios, pregnancy induced hypertension).

Neonatal parameters studied were birth weight, NICU admissions, neonatal death, APGAR scores. Newborns were classified as small for gestational age (SGA) if their birth weight was below the 10th percentile for gestational age according to Brenner et al.(9)

SGA newborns were considered growth retarded if they showed signs of malnutrition (decreased amount of subcutaneous fat, hypoglycemia, hyperbilirubinemia, hypocalcemia, hyperviscosity syndrome) in the immediate neonatal period. Preterm delivery was defined as delivery before 37 completed weeks. Neonatal morbidity was assessed by the length of stay in the neonatal intensive care unit.

We have taken help of Barcelona fetal medicine calculator and perinatology calculators as derivation of MoM and percentile value is required for better prediction than mere numbers.

## RESULTS

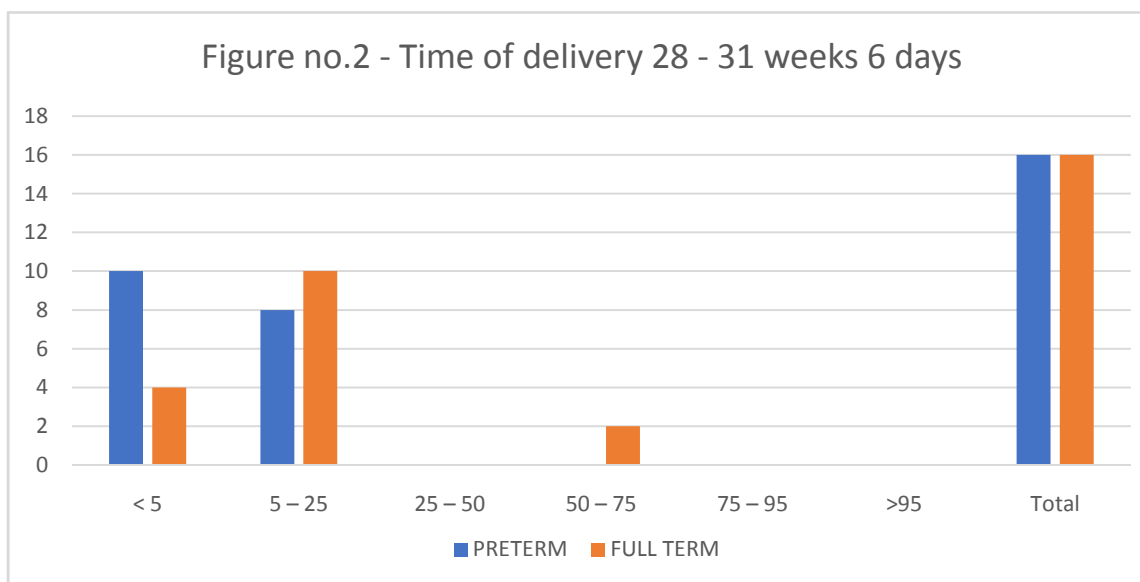
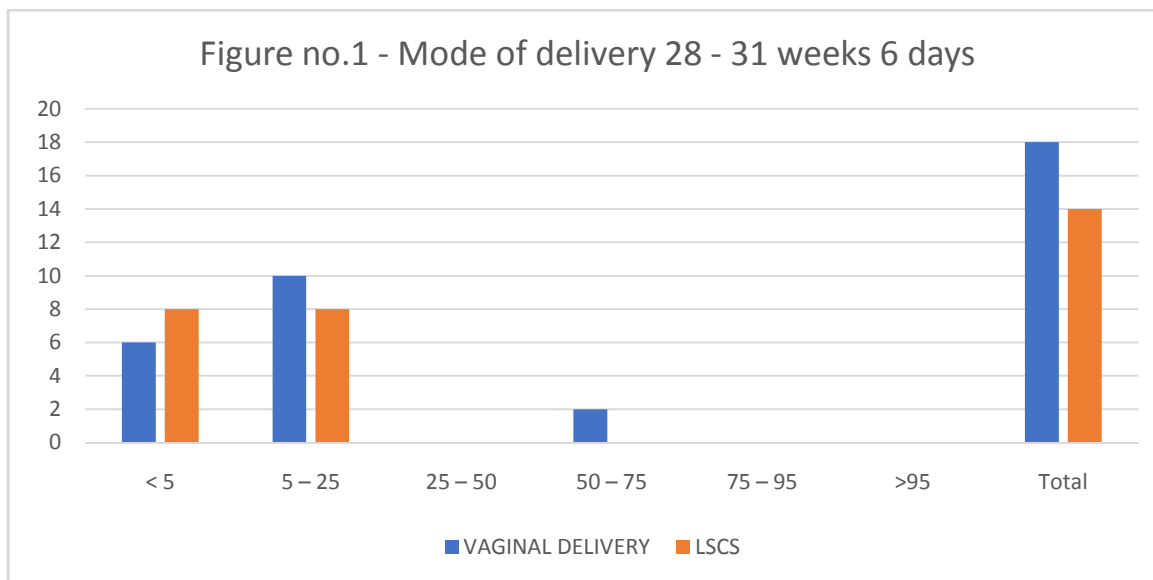
Maternal and perinatal characteristics were evaluated and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

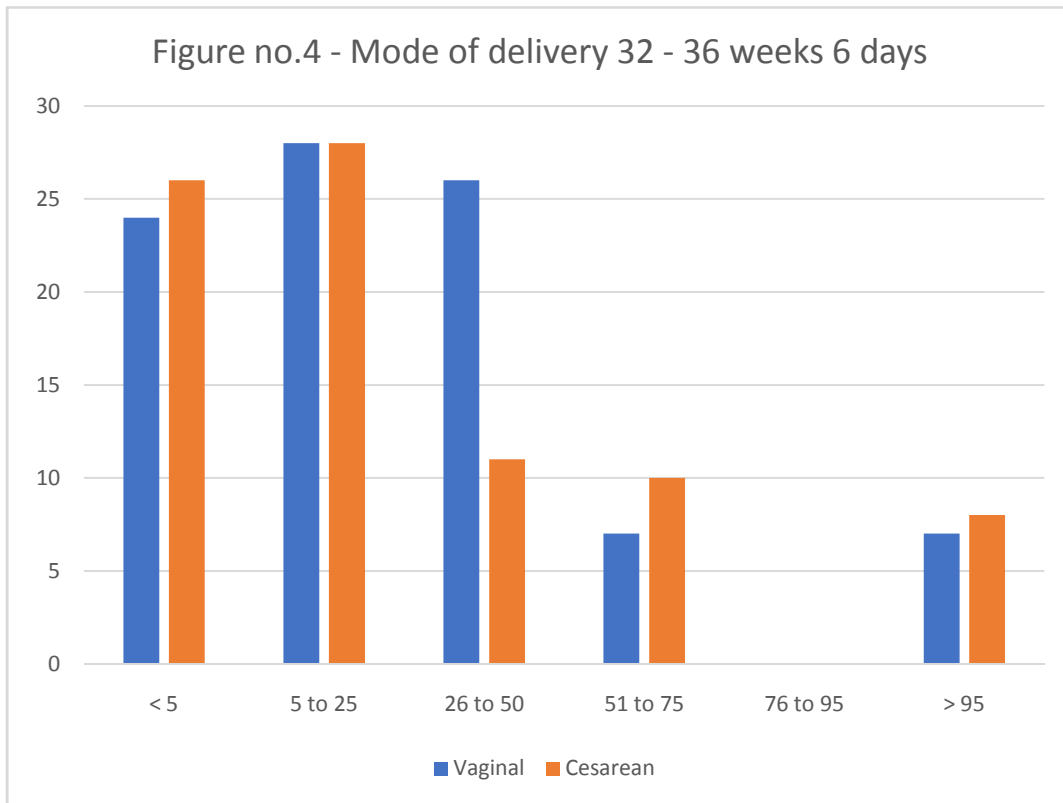
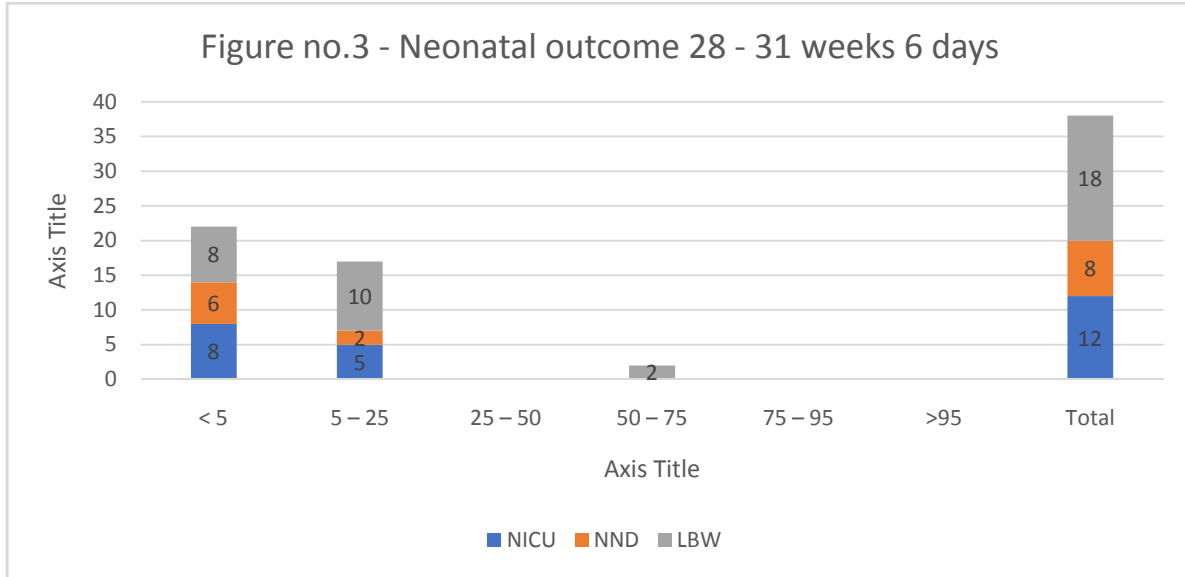
An abnormal CPR was associated with an overall increased for birth by emergency caesarean section (CS). Overall cesarean rate is increased for delivering babies between 28 - 32 weeks gestation irrespective of CPR values possibly due to policy of cesarean section in preterm deliveries. Most of the cases of IUGR in group 37 - 42 weeks have come for first visit.

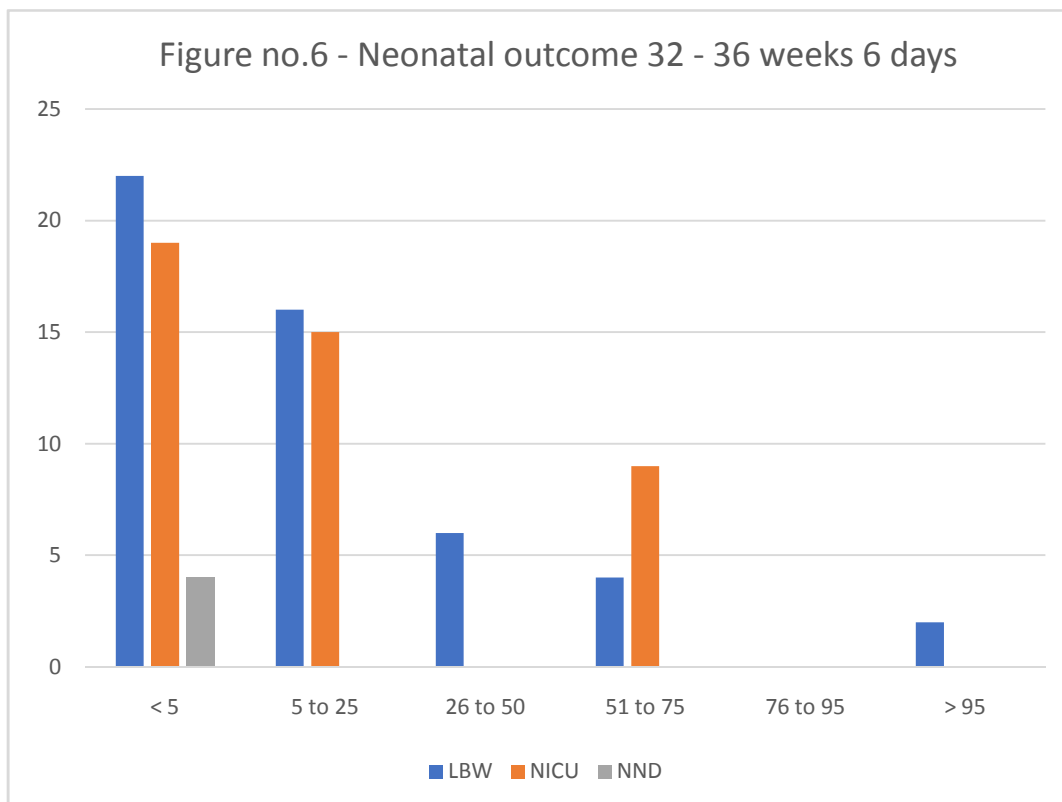
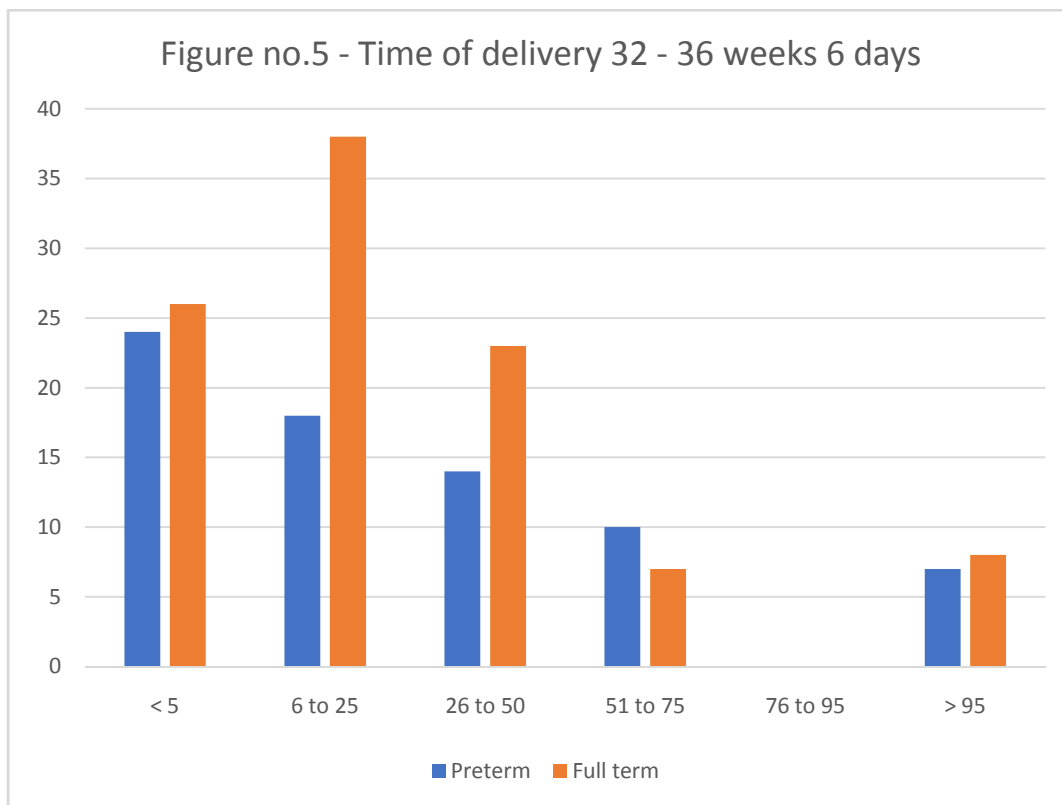
Whereas abnormal CPR values at 28 - 32 weeks, 32 - 37 weeks & 37 - 42 weeks (Figure no. 2 - 8) has shown clear cut increased in cesarean section rate, NICU admission and duration of stay in NICU, Intrauterine deaths, low birth weight.

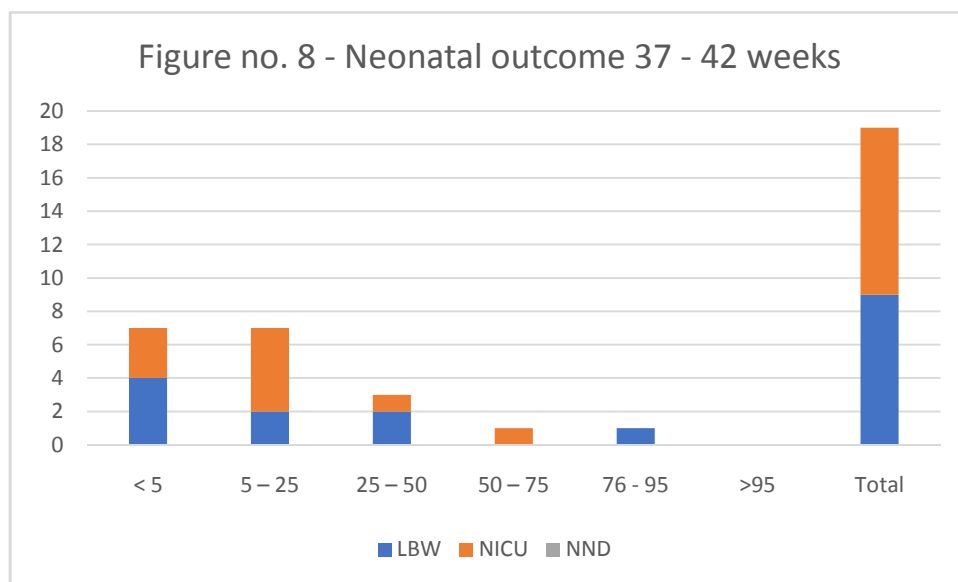
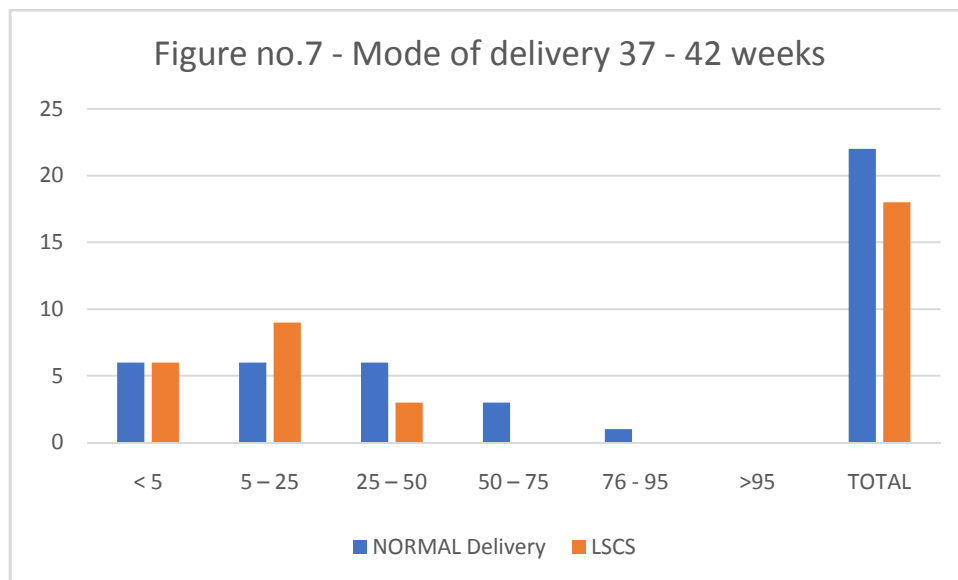
We have categorically identified that CPR values < 5<sup>th</sup> centile and > 95<sup>th</sup> centile increases perinatal morbidity & mortality. We have seen that there is substantial increase in intrauterine and neonatal deaths at < 5<sup>th</sup> percentile .

Khalilet al., 2015 (10) also described the association of low CPR with both instrumental delivery and cesarean section, with the CPR being an independent predictor any operative delivery for intrapartum fetal compromise, irrespective of fetal size. Conversely, a normal CPR was more likely to be associated with spontaneous vaginal delivery.









## DISCUSSION –

When compared to the individual vascular beds, the ratio shows greater variation and appears to offer earlier detection of fetal adaptation to placental insufficiency than either the umbilical or middle cerebral artery. This concept has been explored to predict fetal and/or neonatal compromise using the CPR. (10) Fetuses at 36 weeks' gestation and our previous weeks one at 32 have shown that routine screening by CPR provides poor prediction of indicators for adverse perinatal outcome and it is therefore unlikely that such assessment would improve perinatal outcome. Fetuses with abnormal Doppler results, were delivered by elective Cesarean section and therefore the performance of low CPR in the prediction of Cesarean section for fetal distress in labor would have been underestimated so we have masked the outcome in the interest of the baby. The sensitivity of the CPR from our study is similar to those previously reported for predicting adverse perinatal outcomes in IUGR. In a study by Gramellini et al (11), a CPR of less than 1.08 had a sensitivity of 68% for predicting adverse perinatal outcomes in IUGR. Bahado-Singh et al reported a sensitivity of 63% for predicting adverse outcomes using a CPR transformed



to multiples of the median for each gestational age.(12) Linear regression analysis revealed a strong correlation between the value of the CPR and gestational age at delivery. Kaplan–Meier analysis revealed a significantly decreased latency to delivery (13) . After doing the whole study we have recognize that Intervention thresholds need to be based on the balance of fetal versus neonatal risks and thereforecritically depend on gestational age. Late-onset FGR presents with subtle Doppler and biophysical abnormalities and thereforeposes a diagnostic dilemma. Often unrecognized, termFGR contributes to a large proportion of adverse perinataloutcome. Monitoring intervals should be adjusted based on CPR and middle cerebral artery Doppler and fetal heart rate parameters.Delivery timing thresholds can be low.

## **CONCLUSION**

Abnormal CPR at term was associated with increased need for operative delivery for presumed fetal compromise and admission to the NICU. The CPR has been shown to be a good predictor of the fetal oxygenation status at birth and can be used to identify pregnancies that are at risk for adverse outcomes.

Studies suggest that the CPR is superior to the MCA pulsatility index alone in predicting adverse perinatal outcomes because it reflects acute changes more accurately. Accurate measurement of the CPR is important. Our findings externally validate Baschats nomogram(2) and confirm that the CPR is more effective in predicting adverse perinatal outcomes compared with the individual doppler parameters of MCA and UA.

## **LIMITATIONS**

1. Biases of selective assessment of a population referred for scan assessment at risk, so there will be a slightly higher than the expected proportion of at risk fetuses.
2. The results of the ultrasound and Doppler assessment were not blinded, giving rise to the possibility of subsequent clinical intervention and a ‘treatment effect’ in view of fetal safety.
3. The threshold for the diagnosis of fetal compromise is also likely to have been influenced by changing personnel and attitudes toward intrapartum management.

## **STRENGTH OF STUDY**

1. Single FMF accredited operator using standard protocols with same machine scans to minimize interobserver variation
2. Assessment of outcome data as delivered in the single institute with common local protocol for fetal compromise.

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