A STUDY OF FOETAL AND MATERNAL OUTCOME IN PREGNANCIES WITH IUGR WITH DERANGED DOPPLER

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ABSTRACT

OBJECTIVE
The objective of this study was to study the foetal and maternal outcomes in pregnancies with IUGR and deranged Doppler. And to study the effect of deranged blood flow velocimetry in management of growth restricted pregnancies.

METHODS
This was a prospective study of 96 antenatal women booked at KEM. Hospital Pune during year 2011-2012 between 28-40 wks. of gestation and ultrasonography estimated foetal weight or abdominal circumference < 10th percentile with Doppler velocimetry derangement constituted the study population. Women included in the study were prospectively followed with weekly or biweekly sonography and Doppler velocimetry of maternal Uterine arteries, Foetal Umbilical artery, Middle Cerebral artery. Depending on degree of Doppler derangement daily Non stress test was performed and results were interpreted. Accordingly decision of timing and mode of delivery was taken. Maternal and foetal outcome were studied with respect to mode of delivery in terms of no. of spontaneous or induced vaginal deliveries, no. of Elective caesarean sections, No. of Emergency caesarean sections and neonatal outcome in terms of gestational age at time delivery, no. of live births or stillbirths, APGAR Score at 5 min, birth weight, NICU admission, No. of days of NICU stay, perinatal morbidity and mortality.

RESULTS
23(24%) women underwent Induction of labour, 22(22%) underwent Elective LSCS and maximum 51(53%) women delivered by Emergency LSCS mainly because of non–reassuring foetal heart rate pattern. Live births were 87(90.6%) and 9(9.4%) foetuses were stillborn. Maximum no. 50 out of 87 live born foetuses were <34 weeks of gestation. These neonates had lower birth weight maximum were between 1000-1500gms, all stillbirths had birth weight <1000gms. Out of 87 live births 21(24.1%) had APGAR score <7. Babies with deranged Doppler had more requirement of NICU care 78(89.6%) and for longer duration 31(40%) required >10 days. Total 32 babies had various complications. In the present study, out of 96 study population 9 were stillborn, 11 were Neonatal death, 78 foetuses required NICU care while 32 had complications. Therefore, perinatal mortality is 20(20.8%) and morbidity is 76(79.2 %).

CONCLUSION
The Doppler pattern follow a longitudinal trend with early changes in the Umbilical artery followed by Middle Cerebral artery and other peripheral arteries. Venous changes follow the arterial pattern and occur in severely compromised foetus and predicts poor perinatal outcome. Compared to other methods of foetal monitoring Doppler has proved to be more sensitive in detecting foetal compromise as early and aids in the appropriate timing of delivery. Doppler indices from the foetal circulation can reliability predict adverse perinatal outcome in high risk pregnancy such as intrauterine growth restriction.

KEYWORDS
Doppler Velocimetry, APGAR score, Perinatal Outcome, IUGR.

INTRODUCTION: The normal growth of foetus in the intrauterine life depends on integrity of uteroplacental and foetoplacental circulation. Inadequacy of foetoplacental unit leads to development of intrauterine growth restriction (IUGR).[1] IUGR is most commonly defined as foetus with sonographic estimated foetal weight less then 10th percentile for that gestational age according to Campbell's normogram (Campbell et al 1975, Hadlock et al1982).[2,3]

IUGR[4] has a significant impact on the perinatal mortality and morbidity. It is associated with acidosis, stillbirth, oligohydramnios, low birth weight, prematurity,

antepartum as well as intrapartum foetal distress.[5] Obstetric Doppler study includes the study of uteroplacental and foetoplacental unit.[6]

Uteroplacental study includes: Uterine arteries.
Foetoplacental study includes: Umbilical arteries, Middle cerebral artery, Ductus venosus, Abdominal aorta.

Various circulatory adaptations occur in these vessels as result of growth restriction and it forms the basis to identify such at risk foetuses.[7]

1. Decreased end diastolic velocity in umbilical artery and increase in Systolic/Diastolic ratio, Resistance Index, Pulsatility Index.
2. Increased diastolic flow velocity in intracranial vessel resulting in low S/D ratio in foetal Middle Cerebral Artery.

3. An absence of umbilical artery end diastolic flow.
4. Decreased f et al ductus venosus blood flow and high Pulsatility index. Reversed.
5. Diastolic flow in the umbilical artery.

Progressive knowledge of the foetal circulation and its adaptation when the foetus is subjected to hypoxia, has helped us recognize the early signs of IUGR thereby improving the prognosis of these complicated pregnancies. It has therefore become the gold standard in the management of the growth-restricted foetus.

BASICS OF DOPPLER:
Doppler Effect: The principles of colour flow imaging are based on the Doppler effect (Christian Doppler 1842).[8] Whenever an ultrasound beam with a certain frequency is used to insonate any blood vessel, the reflected frequency is directly proportional to the speed with which the RBCs are moving in that vessel (Blood flow velocity). This frequency shift of the returning signal is displayed on the ultrasound machine screen as a time dependant plot graph, and reflects the events of cardiac cycle.

This is non-invasive method and helps in assessing the foetal wellbeing by detecting the movement of blood flow through the maternal and foetal blood vessels.[9]

Doppler index	Calculation of Doppler index
Systolic/Diastolic Ratio(S/D Ratio) (Stuart 1980)[10]	Peak Systolic Blood Flow/End Diastolic Velocity
Pulsatility index(PI) (Pourcelot 1974)	Peak Systolic Velocity-End Diastolic velocity/Mean Systolic Velocity (S-D/ mean)
Resistance index(RI) (Gosling and king1977)	Peak Systolic Velocity- End Diastolic Velocity/Peak systolic Velocity(S-D/S)
Doppler Indices	

MATERIAL AND METHODS: This was a prospective observational study conducted at KEM Hospital Pune, in the Department of Obstetrics and Gynaecology over duration of 12 months.

Total 96 antenatal women between 28 to 40wks of gestation with IUGR with deranged Doppler indices constituted the study population. Antenatally, IUGR was clinically suspected if fundal height was less than two or more weeks of expected and diagnosis was based on ultrasound parameters with estimated foetal weight being less than 10 th percentile for gestational age or abdominal circumference of foetus below 10th percentile for that gestational age.

Inclusion Criteria:
1. Singleton pregnancy.
2. Pregnant women who were sure of their date of last menstrual periods and had previous regular menses.
3. Foetal gestational age of 28 weeks or more as confirmed with prior first trimester or early second trimester ultrasonography.

4. Ultrasonography estimated foetal weight or abdominal circumference below 10th percentile for gestational age.
5. Doppler Velocimetry showing deranged indices.

Exclusion Criteria:
1. Pregnancy less than 28 weeks.
2. Pregnancy with documented congenital anomalies.
3. Multifoetal gestation.
4. Pregnancy with wrong dates.
5. Rh isoimmunised pregnancy.

The foetal biometry included assessment of biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femoral length (FL). Foetal weight was estimated according to the Hadlock formula that uses FL, AC and BPD.

All these women were prospectively studied with Pulsed wave Doppler sonography of maternal Ut A, foetal UA, MCA after her consent & filling of PNDT form.

PATHOPHYSIOLOGY [11]: The placenta is the lifeline of the foetus and, when challenged, it has a remarkable ability to adapt. Physiological modification of spiral arteries is required to permit the 10-fold increase in the uterine blood flow which is necessary to meet the respiratory and nutritional requirement of the foetus and placenta. It occurs in two stages, the first wave of trophoblastic invasion converts the deciduas segments of the spiral arteries in the first trimester and the second wave converts the myometrial segments in the second trimester.[12] As a result of this "Physiological Change" the diameter of the spiral arteries increases from 15-20 to 300-500mm, thus reducing impedance to flow and optimizing foetomaternal exchange in the intervillous space.

Normal Uterine Artery Doppler: Normal S/D ratio of uterine artery between 28-40wks is 2.6 to 2.2, more than 2.6 is abnormal Normal. RI value for the same is 0.50 at 24 weeks, which gradually reduces to 0.42 till full term.

Pregnancies that result in normal term deliveries show increased diastolic blood flow velocity and loss of the early diastolic notch by 22 weeks of gestation, whereas pregnancies that show persistent high resistance waveforms with early diastolic notches are at risk of preterm delivery from pre-eclampsia, abruption, intrauterine growth restriction and overall higher morbidity as well as mortality.
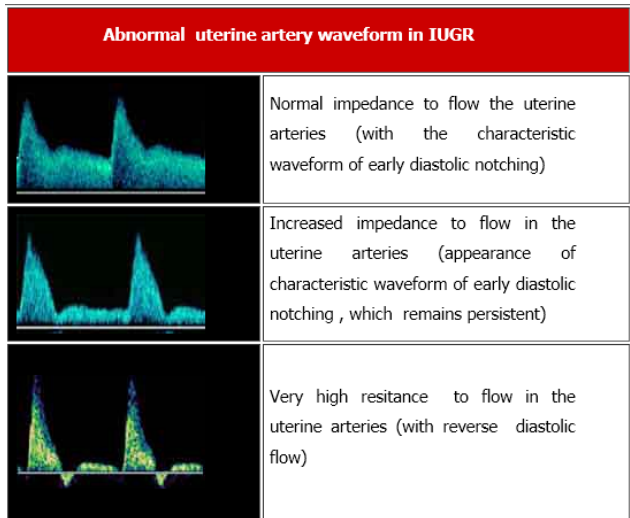
Figure 1

Umbilical Artery: The umbilical artery is the signature vessel in the Doppler study of the foetus as it is a direct reflection of the flow within the placenta.

Normal Umbilical Artery Doppler: Umbilical artery normal S/D ratio between 28-40 weeks is 3 to 2.2, RI is 0.70 to 0.54 and PI is 1.3 to 0.70.

Abnormal Umbilical Artery Doppler: AEDF is a strong and independent predictor of adverse perinatal outcome.
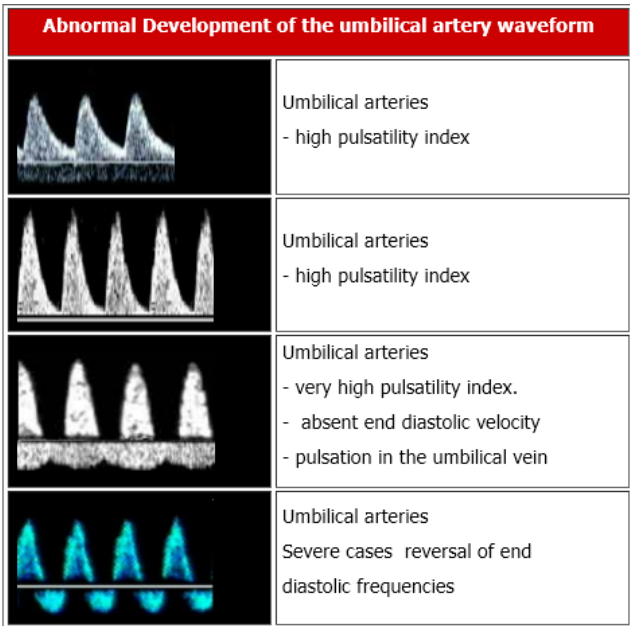

Figure 2

Normal Middle Cerebral Artery Doppler: Normal S/D ratio in middle cerebral artery ranges from 8.4 to 3.8 after 28 weeks of pregnancy. Normal PI is more than 1.5.Normal RI ranges from 0.87 to 0.72.

Abnormal Middle Cerebral Artery Doppler: If there is continued and progressive foetal hypoxia, a phenomenon known as "brain sparing effect" is seen with dilation of the foetal intracranial vessels, which provides increased blood flow to the brain at the expense of other organs. The

presence of such compensation suggests a compromised foetus. With continuing hypoxia, the overstressed foetus loses the brain sparing effect and the diastolic flow returns to the normal level. Presumably, this reflects a terminal decompensation in the setting of acidemia or brain oedema. When brain oedema becomes severe, reversal of diastolic flow maybe seen due to the raised intracranial tension, which suggests grave and irreversible foetal neurological outcome.

Ductus Venosus Doppler: The spectral waveform s described as a classic 'M' pattern characterized by a first and second peak coinciding with ventricular systole and early diastole when there is passive filling of the ventricles. Following this second peak is the nadir before the onset of the next systole. In IUGR when there is progressive hypoxia and worsening contractility of the ventricles and atria secondary to myocardial ischemia, ductus venosus shows a progressive decrease in forward flow due to an increasing pressure gradient in the right atrium. In such cases, tricuspid regurgitation causes a reversal of flow in the inferior vena cava, which eventually leads to reversal of flow in the ductus venosus. Abnormalities in this waveform have been associated with worsening foetal hypoxemia and acidemia, which may precede abnormalities in the foetal heart rate.

OSERVATIONS AND RESULTS: In the present study, maximum women 56 (58.3%) were of the age group 25-29 years, 28(29%) of 20-25 years, 10(10%) women of age <20 years and only 2(2%) were of the age >30 years. The mean age of study population was 25.9 yrs. (SD 3.9). Majority of women 66(68.7%) were primipara, while 30(31.3%) were multipara.

Maximum no. women 59(61.46 %) belonged to gestational age group of <34 weeks, followed by 29(30%) of 34-37 weeks of gestation and 8(8.33 %) had completed term.

Out of 96 women, 73(76%) women had Uterine artery notch, 76(79%) women had Umbilical artery derangement it might be either decreased or absent or reversal of end diastolic flow, and 46(47%) had Middle Cerebral Artery derangement however there was overlapping of deranged Doppler findings.

Doppler derangement	No. of cases	(%)
Only notch	9	9.4
Decreased UA diastolic flow (with or without notch)	26	27
AEDF/REDF in UA with normal MCA	11	11.5
AEDF/REDF in UA with abnormal MCA	21	21.9
Abnormal MCA (with or without notch with decreased end diastolic flow in UA)	29	30.2
Total	**96**	**100.0**
Table 1: Distribution of cases according to groups of Doppler derangement		

58 (60.4%) women had reactive NST and 38 (39.6%) had non-reactive NST.

In present study, total 23 (24%) women underwent induction of labour which includes 6 women who had minimal Doppler derangement such as only Uterine artery notch with reactive NST, and/or completed 37 weeks and 17 women with poor foetal salvageability due to severe IUGR and very LBW (< 1000 gms.). They were induced after due counselling and consent. 22 (22.9%) women underwent Elective LSCS who had deranged Doppler findings in UA or MCA & reactive NST after receiving 2 doses of antenatal steroids. Maximum 51(53%) women underwent Emergency LSCS either due to non-reactive NST & Umbilical artery showing absent or reversal of diastolic flow or MCA showing Brain sparing effect. Worsening of maternal condition due to severe preeclampsia or other medical disorder was an indication of emergency LSCS irrespective of foetal condition.

Foetal Outcome	No. of cases	(%)
Live birth	87	90.6
Stillbirth	9	9.4
Total	**96**	**100.0**

*Table 2: Cases with respect to foetal outcome at time of delivery*

Out of 87 live born babies 66 (75.86%) of babies had APGAR Score >7 and 21(24.14%) babies had APGAR Score <7, 9 of them required endotracheal intubation and 10 required bag and mask ventilation. 38 babies (39.6%) had birth weight in the range of 1000-1500gms, 30(31%) were between 1500-2500gms, while 28(29.2%) had <1000gm birth weight. All stillborn babies had birth weight <1000gms. This observation suggests that very LBW has significant effect on perinatal outcome.

Out of 78 live born babies who required NICU care, 31 (40%) required NICU stay for > 10 days due to prematurity, low birth weight or complications.

Maternal Complications	No. of cases	(%)
Pre-eclampsia	65	67.7
Oligohydramnios	10	10.4
Preeclampsia+Oligo	12	12.5
Anaemia	3	3.1
Chronic Hypertension	3	5.2
HELLP Syndrome	2	2.1
Others	1	1.0

Table 3: Maternal medical complications observed in study population with deranged Doppler

Total 32 babies had various complications, 8 babies had necrotizing enterocolitis, 5 had hypoxic ischemic encephalopathy, 5 had pulmonary haemorrhage, 5 had RDS, 3 had intraventricular haemorrhage, 1 baby had septicaemia while 5 babies had either hypoglycaemia or hyperbilirubinemia. However, some babies had more than one complication.
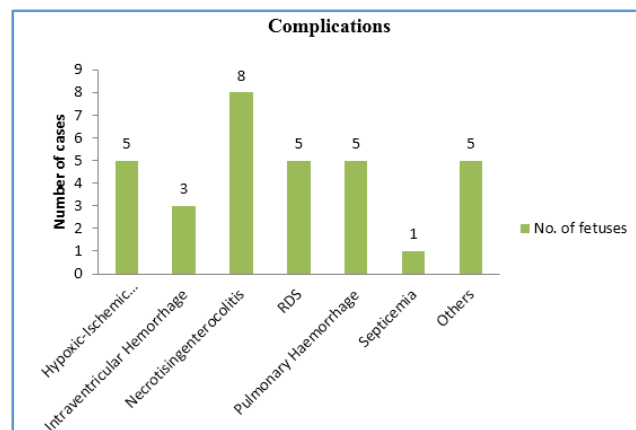
Figure 3

Perinatal Outcome	No. of cases	(%)
NICU Care not required	9	10.3
NICU Care required	78	89.9
APGAR Score at 5 min <7	21	24.1
Emergency LSCS	51	53.1
Stillbirth	9	9.4
Neonatal Death	11	11.5
Neonatal Complications	32	33.3

Table 4: Showing Perinatal Outcome

Women with AEDF/REDF with 7(63.6%) or without (52.4%) MCA abnormality as well as women with MCA abnormality with or without notch with decreased UA diastolic flow 20(68.9%) had significantly more no. of emergency caesarean section compared to women with only notch or decreased UA flow with or without notch. Induction of labour was more common in AEDF/REDF with abnormal MCA 10 (47.6).

Above table shows maximum no. 50 out of 87 live born foetuses were <34 weeks of gestational age, 29 were between 34-37 and 8 were >37 weeks. By using Fisher's exact test p-value <0.05 therefore there is association between gestational ages (weeks) and foetal outcome. All stillborn babies had gestational age <34 weeks.

Women with AEDF/REDF with MCA abnormality had more 4(19.1%) stillbirth followed by women with AEDF/REDF with normal MCA 2(18.2%).Women with only notch had all live births.

Among the above groups, <7 APGAR score was more frequently seen in foetuses with AEDF/REDF with MCA abnormality (41.2%) or without MCA abnormality (33.3%). All foetuses with AEDF/REDF with or without MCA abnormality required NICU admission. Only 2(25%) foetuses with only Uterine notch required NICU >10days, while 18(78.3%) babies with MCA abnormality with or without notch with UA decreased diastolic flow required >10days NICU care. 4(45.5%0 foetuses with AEDF/REDF with normal MCA and 10(58.9%) with abnormal MCA required NICU care.

DISCUSSION: Majority of the women 56(58 %) were of age group of 25-29 yrs and most of them were primi 66(68%). Most of the women 59(61%) were <34 weeks of

gestational age, 29(30%) were of 34-37 weeks and 8(8%) were term.

Among 96 women with deranged Doppler Uterine artery notch was present in 73 women, Umbilical artery derangement in 82 women out of which 50 had decreased diastolic flow, 26 had AEDF and 6 had REDF, while 46 women had MCA derangement. However, they had overlapping of Doppler findings.

Study population was grouped into 5 types depending upon severity of Doppler derangement. 9(9.4%) women had only uterine notch, 26(27%) had decreased UA diastolic flow with or without notch, 11(11.5%) AEDF/REDF in UA with normal MCA, 21(21.9%) had AEDF/REDF in UA with abnormal MCA while 29(29.1%) had Abnormal MCA (with or without notch, decreased end diastolic flow). 65(67%) women had preeclampsia, 2 had HELLP syndrome as complication of severe preeclampsia, oligohydramnios was associated with preeclampsia which constituted 12% of cases with deranged Doppler.

Depending upon the degree of severity of Doppler velocimetry derangement, gestational age of the patient, maternal medical complications such as worsening of preeclampsia, foetal salvageability, NST findings, decision of timing and mode of delivery was taken.

Mode of Delivery: In present study, 23(24%) underwent Induction of labour. These women had either severe IUGR with non-reactive NST suggesting poor foetal salvageability or Doppler velocimetry showing Uterine artery notch with reactive NST in near term or term gestational age group women. 22(23%) women underwent elective caesarean section for Umbilical artery decreased end diastolic flow or AEDF, REDF, with or without Brain Sparing effect with reactive NST. 51(53%) women underwent emergency caesarean section for non- reactive NST with any Doppler findings.

Women with AEDF/REDF with 7(63.6%) or without (52.4%) MCA abnormality as well as women with MCA abnormality with or without notch with decreased UA diastolic flow 20(68.9%) had significantly more no. of emergency caesarean section compared to women with only notch or decreased UA flow with or without notch. Induction of labour was more common in AEDF/REDF with abnormal MCA 10 (47.6).

These observations are comparable to other studies as mentioned in the table below:

Study Conducted by	Year of study	Study Population	Induction (%)	LSCS (%)
Wang KG et al*	1998	30	20	80
BN Lakhkar et al*	2002	58	32	62
Arora et al*	2005	134	17	84
Dhand et al*	2006	121	25	44

Present Study	2012	96	24	76
Table 5				

In present study, maximum patients 61(46%) delivered at gestational age <34 weeks of gestation, followed by 30(21%) in the gestational age group of 34-37 weeks and at term 8(33%).

Foetal Outcome: In present study, foetal outcome is studied in terms of perinatal morbidity and mortality. It includes no. of live births, still births, birth weight, APGAR score, NICU admission, NICU stay >10 days, Neonatal complications and Neonatal death.

Out of 96 women with IUGR with deranged Doppler live births were 87(90.6%) and still births were 9(9.4%). Out of 87 live born babies 11 were neonatal deaths amongst NICU admitted babies due to complications such as HIE, NEC, RDS, Septicaemia during NICU stay.

Women with AEDF/REDF with MCA abnormality had more 4(19.1%) stillbirth followed by women with AEDF/REDF with normal MCA 2(18.2%) and 2(6.9%) MCA abnormality with or without notch and UA decreased diastolic flow, 1(3.9%) stillbirth with decreased UA flow. Women with only notch had all live births.

These findings are comparable to following studies;

Study conducted by	Year of study	Study population	Live births (%)	Stillbirths (%)	NNDs (%)
Katherine W Fong	1997	293	95	4	1.3
Wang K G et al *	1998	30	50	10	44
B N Lakhhan et al	2002	58	79	9	12
Present Study	2012	96	91	9	11
Table 6					

Birth Weight: 38(40%) had birth weight in the range of 1000 – 1500gms, followed by 30(31%) in the range of 1500 -2500gms, and 28(29%) babies had <1000 gms. All stillborn foetuses had birth weight < 1000 gms. Severely compromised uteroplacental flow leads to severe IUGR and hence birth of very low birth weight babies.

Gestational Age: In this study, maximum no. 50 out of 87 live born foetuses were <34 weeks of gestational age 29 were between 34-37 and 8 were >37 weeks. Present study shows that there is association between gestational age (weeks) and foetal outcome. All still birth babies had birth weight <1000gms.

APGAR score: In present study, APGAR score <7 was more frequently seen in foetuses with AEDF/REDF with MCA abnormality (41.2%) or without MCA abnormality (33.3%). 9 foetuses among them, were intubated and 10 babies required bag and mask ventilation. This shows that severity of Doppler derangement corresponds with APGAR score

NICU Admission: In present study, 78 (90%) babies out of 87 live born required NICU Care either due to LBW and or prematurity and among them 32 (41%) babies had > 10 days NICU stay.

All foetuses with AEDF/REDF with or without MCA abnormality required NICU admission. 23(85.1%) foetuses with MCA abnormality with or without notch with decreased diastolic flow. 8(88.8%) foetuses with notch and 21(84%) foetuses with decreased UA diastolic flow required NICU admission. This shows that degree of derangement of Doppler velocimetry is associated with NICU care requirement.

NICU Stay: In the present study, out of 78 live born babies who required NICU care,31 (40 %) required NICU stay for > 10 days due to prematurity, low birth weight or complications.

Neonatal Complications: In present study, 32(33.3%) babies out of 78 NICU admissions suffered from complications like Hypoxic Ischemic Encephalopathy Grade III/ IV, Intraventricular Haemorrhage, Necrotising Enterocolitis, Pulmonary Haemorrhage, Septicaemia, Hypoglycaemia and eventually there were 11 neonatal deaths amongst NICU admitted babies due to complications mentioned above.

Present study is comparable to:

Study conducted by	Year of study	Study population	NICU admissions (%)	NICU stay >10 days (%)	Neonatal complications
Katherine WFong et al *	1997	293	54	45	26
B N Lakhkar et al *	2002	58	66	43	32
Arora et al *	2005	134	80	-	14
Present Study	2012	96	90	40	33
Table 7					

In the present study, out of 96 study population 9 were stillborn, 11 were Neonatal death, 78 foetuses required NICU care while 32 had complications. Therefore, overall perinatal mortality is 20 (20.8%) and morbidity is 76 (81.2%).

In IUGR foetuses, reversal of flow in the Ductus venosus is an ominous sign.

In present study, only one patient had reversal of DV flow in Doppler study and foetal outcome was stillbirth.

CONCLUSION: The Doppler pattern follow a longitudinal trend with early changes in the umbilical artery followed by middle cerebral artery and other peripheral arteries. Venous changes follow the arterial pattern and occur in severely compromised foetus and predicts poor perinatal outcome. Doppler indices from the foetal circulation can reliability predict adverse perinatal outcome in high risk pregnancy such as intrauterine growth restriction.

AEDF/REDF represents an ominous and severe foetal condition with an adverse pregnancy outcome, especially in conditions associated with intrauterine growth restriction and/or preeclampsia. Intensive and frequent surveillance and aggressive management at the appropriate time would improve perinatal outcome.

Doppler velocimetry along with conventional methods of antenatal foetal monitoring such as NST plays an important role in monitoring the growth restricted foetus and thereby helps to determine the optimal time and mode of delivery.

REFERENCES:

1. Fernando A, Daftery S. Foetal growth restriction, Practical guide to high risk pregnancy and delivery. 3rd edition:105-134.
2. Campbell S, Wilkin D. Ultrasonograghic measurement of foetal abdominal circumference in the estimation of foetal weight. Br. J Obstet Gynecol 1975;82(9):689-97.
3. Hadlock FP, Deter RL, Harrist RB. Foetal abdominal circumference as predictor of menstrual age. Am J Radiology 1982;139:367-70.
4. Nyberg DA, Abuahemad A, Ville Y. Ultrasound assessment of abnormal foetal growth. Seminars in perinatology 2004;28:3-22.
5. Smith–Bindman R, Chu PW, Ecker JL, et al. US evaluation of foetal growth: predictors of neonatal outcomes. Radiology 2002;223:153-61.
6. Kevin A, Mairi H, James P, et al. Pregnancy screening by Doppler, uteroplacental and umbilical artery waveforms. Br. J Obstet Gynecol 1989;96:63-67.
7. Trudinger BJ. The principles and practice of ultrasonography in OBGY. Obstetric Doppler Application: 4th edition;12:173.
8. White DN, Christian J. Doppler and his effect–A brief history. Ultrasound Medicine and Biology 1982;8:583-591.

9. Fitz Gerald DE, Drumm JE. Non-invasive measurement of human foetal circulation using ultrasound: a new method. Br Med J. 1977;2(6100):1450-1.

10. Stuart B, Drumm J, Fitz Gerald DE, et al. Foetal blood velocity waveforms in normal pregnancy. Br J Obstet Gynaecol 1980;87(9):780-5.

11. Mandruzzato GJ. Perinatal medicine-intrauterine growth restriction. (IUGR), 01- January, 2008;36(4). (Medline).

12. Brosens I, Robertson WB, Dixon HG. The physiological response of the vessels of the placental bed to normal pregnancy. J Pathol Bacteriol 1967;93:569-79.