Doppler changes as the earliest parameter in fetal surveillance to detect fetal compromise in intrauterine growth-restricted fetuses

Saloni Bansal[1], Deepika Deka[2], Vatsla Dhadwal[2], Rajiv Mahendru[1]

[1]Department of Obstetrics and Gynaecology, BPS Government Medical College for Women, Khanpur Kalan (Sonepat), Haryana, India;
[2]Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, India

SUMMARY

Introduction It is estimated that 3–10% of infants are growth restricted. Growth disturbances may have long-term issues. Doppler allows insight into the fetal response to intrauterine stress.

Objective The aim of this study was to detect fetal compromise in intrauterine growth-restricted (IUGR) fetuses by means of biophysical profile (BPP) *vis-à-vis* Doppler velocimetry studies of the fetal umbilical artery, and to find out which of the two is a better and earlier predictor of fetal compromise.

Methods A prospective study was conducted on a total of 50 singleton pregnancies with IUGR between 28 and 42 weeks of gestation. Study patients were managed expectantly with nonstress testing and amniotic fluid assessment, BPP and Doppler velocimetry studies of the fetal umbilical artery.

Results Fetal outcome was poor in 5/50 (10%) of the fetuses, defined as presence of all of the following: poor Apgar test score, neonatal intensive care unit stay, necrotizing enterocolitis, and low birth weight. Of the four with abnormal BPP, 50% had poor fetal outcomes. Out of 46 with normal BPP, 6.5% had poor fetal outcomes.

Conclusion Inference drawn from the study is that the Doppler technology provides us the opportunity for repetitive noninvasive hemodynamic monitoring in IUGR pregnancies.

Keywords: intrauterine growth restricted; Doppler; fetal compromise

INTRODUCTION

Intrauterine growth-restricted (IUGR) fetuses are those whose birth weight is below the tenth percentile of the average for the gestational age. It is estimated that 3–10% of infants are growth-restricted. Ultrasound evaluation is considered the cornerstone of diagnosis and surveillance of fetuses with intrauterine growth restriction [1]. Growth disturbances may have long-term issues. These infants are at risk of developing asphyxia, respiratory distress syndrome, hypoglycemia, hypothermia, pulmonary hemorrhage, polycythemia, necrotizing enterocolitis (NEC), and intraventricular hemorrhage, as well as long term consequences. For fetuses remote from term, strict antenatal monitoring and timely intervention are the key components. The most common testing modalities used include the biophysical profile (BPP), nonstress testing (NST), amniotic fluid analyses, and examination of fetal blood vessels using Doppler velocimetry [2].

IUGR fetuses are of two types: symmetric and asymmetric. Symmetric ones can be caused by intrauterine infection or chromosomal abnormalities. Asymmetric ones are due to maternal vascular diseases causing placental insufficiency resulting in decreased blood flow through the umbilical vessels to the fetus.

BPP involves combined use of five fetal biophysical variables, namely NST, fetal breathing movement, gross body movement, fetal tone, and amniotic fluid volume, making a total score of 10. Fetal hypoxia leads to damping of normal neuronal discharge resulting in cessation of normal function. Average duration of sleep–wake cycles in the normal fetus in approximately 20 minutes; hence BPP takes 30 minutes to account for normal variations.

Doppler is a non-invasive technique to assess blood flow by characterizing downstream impedance. It allows insight into the fetal response to intrauterine stress. In normal pregnancies, umbilical artery (UA) resistance shows continuous decline, in contrast to fetuses with uteroplacental insufficiency. Systolic-to-diastolic ratio is the most commonly used measure of gestational age-specific UA resistance, which changes from a baseline to an elevated value with disease worsening. With progress of the disease, end-diastolic velocity is lost and, finally, reversed. Previously the only marker of an adverse perinatal outcome were reduced end diastolic flow (REDF) or absent end diastolic flow (AEDF); more recently, flow patterns are also being used as markers of fetal wellbeing. Other vessels and venous Doppler also provide information of the fetal response to intrauterine environment.

Using Doppler as a mode of fetal surveillance, there were significant reductions in the induction of labor in elective deliveries, in cesarean sections for fetal distress, and in ante-

Correspondence to:
Rajiv MAHENDRU
Department of Obstetrics and Gynaecology
BPS Government Medical College for Women
Khanpur Kalan (Sonepat), Haryana
India
dr.rmahendru@gmail.com

partum admissions to the hospital. Moreover, Doppler is a less time-consuming method than BPP. These positive effects occurred without evidence of adverse effects [3].

OBJECTIVE

The aim of this study is, hence, to find out which of the two is the better and earlier predictor of fetal compromise.

METHODS

This is a prospective study conducted over two years, from November 2011 to October 2013 in the Department of Obstetrics and Gynaecology at a reputed Institute of Medical Sciences in India. A total of 50 singleton pregnancies between 28 and 42 weeks of gestation with IUGR constituted the study population. Those with multiple gestations and anomalous fetus were excluded. The study was approved by the departmental Ethics Committee.

Patients who were enrolled in the study were worked up in detail, including the previous obstetric information. Record of general physical, obstetrical examination and routine antenatal investigations was kept.

IUGR fetuses were defined according to ultrasound parameters as the ones with estimated fetal weight less than the 10th centile for gestational age. Estimated fetal weight was calculated using Hadlock's formulae using following fetal parameters: parietal diameter, abdominal circumference, head circumference, and femur length. Parietal diameter can be appropriately measured through any plane of section that traverses the third ventricle and thalami. The margins of the calvaria must be symmetrical. For head circumference, correct plane of section is through the third ventricle and thalami in the central portion of the brain, but cavum septum pellucidum must be visible in the anterior portion of the brain and tentorial hiatus in the posterior portion. For femur length, proper plane is the one where both the femoral head of greater trochanter and femoral condyle are simultaneously in the plane of the section. Exclude cartilaginous ends during measurement and place cursors at junction of cartilage and bone. Fetal abdominal circumference is measured at the portion where the transverse diameter of the liver is greatest. Correct plane is the portion where the right and left portal veins are continuous with one another and appearance of lower rib is symmetrical. The fetuses that weighed less than the 10th centile were subjected to weekly Doppler and BPP. Scan also included a general survey of fetal position, a confirmation of cardiac activity, and an assessment of amniotic fluid volume. Acute fetal biophysical variables (breathing, movement, and tone) are assessed as normal or abnormal against fixed criteria and given a score of 2/2 or 0/2, respectively.

Study of fetal umbilical arteries was performed using LOGIQ 700-GE pulsed Doppler ultrasound (Medical systems, Waukesha, Wisconsin, USA) with 3.5 MHz curvilinear probe with a high-pass filter. Measurements were made from free loop of cord with the fetus in resting condition. Position of the umbilical cord was initially identified on real time ultrasound and a segment of the cord was chosen from where the measurement had to be taken. Color was then put on the chosen vessel. Once the cursor was on the vessel, with the help of pulsed wave, Doppler waveforms were obtained and Doppler parameters calculated – resistance index, pulsatility index, systolic/diastolic ratio (S/D).

Study patients were managed expectantly with NST and amniotic fluid assessment, BPP and Doppler velocimetry studies of the fetal UA weekly or biweekly. The frequency of testing was increased if the fetal tests were non-reassuring. Result of the last Doppler examination within three to seven days of delivery was considered in the subsequent correlation with perinatal outcomes. These babies were followed up postnatally to see their outcome in terms of birth weight, at birth complications like birth asphyxia, meconium aspiration, and others, like the need for and length of stay in neonatal intensive care unit (NICU), and also latter complications like NEC. Adverse neonatal outcome included admission to the NICU, respiratory distress requiring ventilatory support, need for total parenteral nutrition, sepsis, NEC. Presence of all the aforementioned criteria defined abnormal perinatal outcome.

Delivery was expedited in case of nonreassuring tests of fetal wellbeing, defined as AEDF or REDF in the UA. Elective cesarean delivery was performed in the presence of nonreassuring fetal tests.

Statistical analysis

Data were presented as number (%) or mean ± SD, as appropriate. Receiver operating characteristic (ROC) curve was used to find out the cut-offs for BPP and color Doppler, considering fetal outcome as the gold standard. The results are presented as sensitivity, specificity, and positive and negative likelihood ratios. All statistical analyses was carried out using STATA 9.0 (College Station, Texas, USA).

RESULTS

A total of 50 patients were recruited into the study, who met the inclusion criterion and were detected to have IUGR at the time of recruitment. Mean age of the study population was 24.3 years and 30% were primigravida. Mean period of gestation at recruitment was 33 weeks. Gestational hypertension was seen in 20%, antiphospholipid antibody in 6%, thrombophilia in 4%, autoimmune disorders in 4%, recurrent urinary tract infection in 2%.

Various other characteristics like the ultrasound parameters to define IUGR pregnancies and color Doppler parameters of the Umbilical artery (UA) were studied. At baseline, all had a BPP score of 10. Doppler parameters were within normal range. Tables 1 and 2 provide the mean values of above parameters.

The fetal outcomes of these IUGR pregnancies were studied in terms of birth weight, birth asphyxia, Apgar

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Table 1. Baseline characteristics in pregnancies with intrauterine growth restriction (IUGR)

Parameter		Mean±SD
Period of gestation (weeks)		33.24±1.7
Umbilical artery	Resistance index	0.61±0.19
	Pulsatility index	1.34±0.36
	Systolic/diastolic ratio	2.67±0.24
Middle cerebral artery	Resistance index	0.82±0.23
	Pulsatility index	1.57±0.47
	Systolic/diastolic ratio	4.01±0.88
Lag (weeks)	Biparietal	1.6±0.88
	Abdominal circumference	2.9±0.81
	Femur length	1.78±0.78
Liquor		8.82±1.77

SD – standard deviation

Table 2. Characteristics before termination in pregnancies with IUGR

Parameter		N	Fetal outcome	
			Good	Poor
Doppler results	S/D <3	35	35	0
	Raised S/D	4	4	0
	AEDF	6	4	2
	REDF	3	1	2
	DV reversal	2	1	1
Biophysical profile	>6/10	46	43	3
	6/10	2	2	2
	4/10	1		
	2/10	1		

N – number of patients; S/D – systolic/diastolic ratio; AEDF – absent end diastolic flow; REDF – reversal end diastolic flow; DV reversal – ductus venosus flow reversal

Table 3. Doppler parameters and biophysical profile score in poor outcome fetuses

Poor outcome fetuses	Doppler value	BPP value
1	REDF	10/10
2	Ductus venosus flow reversal	10/10
3	AEDF	4/10
4	AEDF	10/10
5	Ductus venosus flow reversal	6/10

BPP – biophysical profile; REDF – reversal end diastolic flow; AEDF – absent end diastolic flow

score, meconium aspiration, NICU stay and NEC. Forty-three (86%) babies weighed <2.5 kg at birth. An Apgar score of <9/9 was found in 10/50 (20%), 17/50 (34%) stayed in NICU and 7/50 (14%) developed NEC. Out of these seven who developed NEC, 45% had AEDF, 28% had REDF, and another 27% had flow reversal in ductus venosus (Table 2).

Fetal outcome was poor in 5/50 (10%) of the fetuses, defined as presence of all- poor Apgar, NICU stay, NEC and low birth weight. Of the 4 with abnormal BPP, 50% had poor fetal outcomes. Out of 46 with normal BPP, 6.5% had poor fetal outcomes. All 5/5 fetuses with had an abnormal Doppler was found in all the fetuses with poor outcome. We found that amongst 5 with poor outcomes, 40% had AEDF, 40% had REDF and 20% had flow reversal in ductus venosus (Table 3).

AS described in Table 2 out of 50 fetuses, 35 had normal Doppler results; 4 had raised S/D ratio meaning minimally compromised; 6 had AEDF; 3 each were of REDF and reversal of ductus venosus flow meaning severely compromised. But all these severely compromised did not land up in poor fetal outcome. Likewise for biophysical profile 46 fetuses out of 50 had a score of 8/10 or 10/10 ie either single or at the most two components were affected. Among the remaining four, two had score 6/10 and one each had a score of 4/10 and 2/10. And all these fetuses with score 6/10 or less had poor outcomes. During serial Doppler velocimetry and BPP it was found that Doppler became abnormal 10–14 days prior to BPP.

The ROC analysis revealed AEDF in UA as optimal cut-off that provides an ROC area of 0.95 (95% CI, 0.89–1.00). The ROC analysis revealed a BPP score of 10/10 as optimal cut-off that provides an ROC area of 0.67 (95% CI, 0.43–0.91) (Table 3).

DISCUSSION

IUGR refers to a condition in which a fetus is unable to achieve its genetically determined potential size. This functional definition seeks to identify a population of fetuses at risk for modifiable but otherwise poor outcomes. Accurate and effective monitoring of fetal growth is one of the key components of prenatal care.

In pregnancies with IUGR, gestational hypertension was seen in 20%, chronic in 4%, antiphospholipid antibody syndrome in 6%, thrombophilia in 4%, autoimmune disorders in 4%, recurrent urinary tract infection in 2%, and unexplained in 60% of patients in the present study. The leading causes which have been identified in other studies also included hypertension, diabetes, antiphospholipid antibody syndrome, chronic systemic diseases and unexplained causes in 50% of patients, which is consistent with the present study [2].

Antepartum fetal testing has been a matter of great concern among the obstetricians. Over time, various methods have been devised, used, studied, and critically analyzed in order to get a better predictor for perinatal outcome. Our study of antenatal testing for IUGR fetuses revealed that having an abnormal Doppler study in the presence of IUGR is associated with the highest risk of abnormal fetal outcome, compared with patients who have a non-reassuring NST or BPP. In IUGR, first there is decreased diastolic flow in the UA due to increase in the resistance that occurs in small arteries and arterioles of the tertiary villi. This raises the S/D ratio; Pl and Rl of UA. As the placental insufficiency worsens, the diastolic flow decreases, then become absent, and later reverses.

Using Doppler as a mode of fetal surveillance, there were significant reductions in the induction of labor, in elective deliveries, in cesarean sections for fetal distress, and in antepartum admissions to the hospital. These positive effects occurred without evidence of adverse effects [3].

Fetal outcomes of these IUGR pregnancies were studied in terms of birth weight, birth asphyxia, Apgar score, meconium aspiration, NICU stay and NEC. Fetuses with all of these parameters were considered to have poor or abnormal

Table 4. Diagnostic accuracy of biophysical profile in predicting adverse perinatal outcome

Study [ref. No]	Sensitivity	Specificity	PPV (%)	NPV (%)
Present study	40	96	50	93
Gonalez et al. [6]	19	96	64	79
Tongprasert et al. [7]	50	99.07	50	99.07
Piazze et al. [8]	80	58	28	83

PPV – positive predictive value; NPV – negative predictive value

Table 5. Diagnostic accuracy of Doppler in predicting adverse perinatal outcome

Study [ref. No]	Sensitivity	Specificity	PPV (%)	NPV (%)
Present study	100	77.78	33	97
Lakhkar et al. [9]	75	41.3	25	86.3
Maulik et al. [10]	79	93	83	91
Romero et al. [11]	28	97	40	96.2

perinatal outcome. All these poor fetal outcomes were better predicted by Doppler rather than BPP. The diagnostic accuracies of both these tests are given in Tables 4 and 5.

We found that all fetuses with poor outcome had abnormal Doppler results. The sensitivity of Doppler (cut-off taken to be AEDF) for poor fetal outcome was found to be 100%. This means that all the fetuses with poor fetal outcomes could be identified by poor Doppler results. In other words, the pick-up rate of abnormal Doppler results for poor fetal outcome is 100%, whereas a normal Doppler reading could correctly identify 77.78% of the fetuses as being normal, thus avoiding unnecessary admissions and early inductions. This means a reduction in the load of caesarean sections, as well as elective deliveries done in view of other antenatal tests. Also, the ability of a normal Doppler to predict a good fetal outcome was found to be 97%.

With increasing severity of abnormal Doppler, false positivity rate decreases. Best UA-S/D cut-off for screening is AEDF. As UA-S/D worsens, although specificity increases, sensitivity falls. Nicolaides et al. [4] found that 70–80% of the fetuses with AEDF were hypoxic, and 45% acidotic. Yoon et al. [5] demonstrated in their study that absent umbilical artery waveform is a strong and independent predictor of adverse perinatal outcome.

The ability of an abnormal BPP, a score of <6/10 to predict a poor fetal outcome was found to be 50%, and the ability of a normal BPP to predict a good fetal outcome was 93%. It was also established that 40% of the fetuses with poor fetal outcomes could be correctly identified by poor BPP in comparison to the 100% pick-up rate for Doppler. However, since 96% of the fetuses with good fetal outcomes could be identified by a normal BPP, this highlights that BPP is a good 'rule out' test of poor fetal outcome.

Another important inference drawn was that Doppler could pick up fetal compromise earlier than BPP. Amongst the five patients with poor fetal outcomes all had an abnormal Doppler, but only 40% had abnormal BPP before delivery. This highlights that while BPP was still normal, fetuses were already at compromise, as confirmed postnatally by the presence of parameters for abnormal perinatal outcome, like nursery admissions and development of NEC, but these were correctly identified antenatally by abnormal Doppler. This means that Doppler is an earlier predictor of poor neonatal outcome.

To plan the most appropriate timing of delivery for the preterm severe IUGR fetus is the most crucial part in the management of these fetuses. The optimal antepartum test to determine this is the greatest dilemma. However, our data suggests that fetal Doppler studies may improve the efficiency and efficacy of antenatal testing in preventing morbidity and mortality of IUGR fetuses, compared to BPP.

CONCLUSION

Doppler technology provides us the opportunity for repetitive noninvasive hemodynamic monitoring in IUGR pregnancies. There is sufficient evidence that Doppler indices from the fetal circulation can reliably predict adverse perinatal outcome in an obstetric patient population with fetal growth restriction. According to the present study, Doppler proved to be more sensitive in detecting fetal compromises and could reliably predict poor outcomes in the form of birth weight, birth asphyxia, Apgar score, NICU stay, and NEC. AEDF was found to be the best UA-S/D cut-off for screening. With increasing severity of abnormal Doppler, false positivity rate decreases. It also detects fetal compromise early and can aid in the appropriate timing of delivery. We made comparisons of BPP and Doppler with the immediate neonatal outcomes only, and no long-term follow-up, which may be beneficial in identifying the long-term complication to which these babies are predisposed to, was done.

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Промене на доплеру као најранији показатељ у праћењу фетуса за установљавање угрожености плодова с интраутерусним застојем у расту

Салони Бансал[1], Дипика Дека[2], Ватсла Дхадвал[2], Рајив Махендру[1]

[1]Одељење за акушерство и гинекологију, Државни медицински колеџ за жене БНП, Кханпур Калан, Сонепат, Харјана, Индија;
[2]Одељење за акушерство и гинекологију, Свеиндијски институт за медицинске науке, Њу Делхи, Индија

КРАТАК САДРЖАЈ

Увод Процењује се да 3–10% новорођенчади пати од интраутерусног застоја у расту (ИУЗР). Сметње при расту могу имати дугорочне последице. Доплер дозвољава увид у реакцију фетуса на интраутерусни стрес.

Циљ рада Сврха ове студије била је да се открије угроженост плодова са ИУЗР помоћу биофизичког профила (БФП), као и велосиметријским испитивањем фетусне пупчане артерије помоћу доплера, како би се установило која је од ове две методе бољи и ранији показатељ угрожености плода.

Методе рада Проспективна студија је обухватила 50 једноплодних трудноћа са ИУЗР у 28–42. недељи гестације. На испитанице обухваћене студијом примењен је експектативни поступак, са испитивањем без стреса и провером амнионске течности, као и БФП-ом и велосиметријском анализом фетусне пупчане артерије помоћу доплера.

Резултати Исход је био неповољан код пет фетуса (10%), што је дефинисано присуством свих набројаних показатеља: лоша оцена на Апгар тесту, боравак на одељењу неонаталне интензивне неге, некротизирајући ентероколитис и мала телесна маса на рођењу. Од четири случаја са абнормалним БФП, фетални исход је био неповољан у 50%. Од 46 случајева са нормалним БФП, 6,5% је имало неповољан фетални исход.

Закључак На основу резултата истраживања може се закључити да нам технологија доплера пружа прилику за понављање неинвазивног праћења хемодинамике у трудноћама са ИУЗР.

Кључне речи: интраутерусни застој у расту; доплер; угроженост плода

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