



Prediction of Intrauterine Growth Restriction (IUGR) using Novel Method of Non-invasive Doppler Ultrasound - A Systematic Review

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ABSTRACT

Based on the systematic review, periodic Doppler assessment is essential in IUGR. However, there is no novel method to detect the various anomalies of IUGR. Therefore there is a need to conduct further reviews on non-invasive Doppler study for identifying all the methods. Intrauterine growth restriction (IUGR) caused by various etiologies results in an increased risk of perinatal mortality and morbidity. This paper systematically reviews the various methodologies adopted in predicting growth restriction and its fetal outcome. A systematic search of articles (PubMed, Scopus, Google scholar, CINAHL and Web of Science) was undertaken for English language articles which were published between 1st June 1986 and 31st December 2013. Total 2049 articles related to the topic was searched and finally, 11 articles are selected. A total of eleven articles are included in the review. The Doppler study included were an umbilical artery, middle cerebral artery, aortic isthmus, descending thoracic artery and ductus venous flow. Pulsatility index (PI), resistivity index (RI) and S/D ratio are studied by various authors. The Doppler flow predicts the adverse effect of the fetal outcome in IUGR and non-IUGR group. A review highlighted that periodic Doppler assessment in IUGR has the effective tool in assessing the hemodynamic state of the fetus and abnormal patterns that predict the adverse perinatal outcome. This engages the IUGR subjects in close monitoring and helps in minimising perinatal complications.

Keywords: Intrauterine growth restriction, Umbilical artery Doppler, Middle cerebral artery Doppler, Descending aortic Doppler, Aortic Isthmus Doppler, Fetal outcome.

INTRODUCTION

IUGR is the common presenting problem during pregnancy accounting for approximate 4 to 7 % of incidence which interferes variable with the neonatal outcome. Even though IUGR prevalence is very high, there is a need to conduct a systematic review to analyse and report the existing method of Doppler assessment for early detection.

Pregnancy complicated by IUGR may possess a wide range of fetal/neonatal compromise. The diagnosis of IUGR is done based on the presence of weight small for gestational age (SGA), with estimated fetal weight of lesser than that of 10th percentile from the reference population. SGA per-se does not hold accuracy for the diagnosis of IUGR since it is limited by confounding maternal constitutional parameters that affect the weight of fetus without compromising the fetal growth (1-3). This ensures the need for the assessment of additional parameters in IUGR that can predict adverse outcome in the neonate, which directs the treatment options for management. These parameters include maternal demographic assessment, geographical impact, Doppler flow pattern in arteries and ductus venous. In emerging techniques, Doppler assessment in fetus plays a major role in assessing abnormal flow pattern in the different site of vessels. Few studies have proven the presence of

abnormal flow pattern in the descending aorta, aortic isthmus, ductus venous, cerebral arteries etc. among IUGR cases in comparison to normal pregnancies with certain evidence of predicting the adverse outcome in neonates (4, 5). Hence to identify the cases with IUGR, fetal Doppler flow assessment of cerebral artery, umbilical artery and aorta will hold the needful tool. Literature does not show any conflicts in the selection of single vessel of choice in Doppler assessment with its interference with the altered load. This review discusses the outcome of certain studies specific for the arterial Doppler assessment in IUGR.

METHODS

Search strategy and selection criteria: The studies were identified by using a comprehensive search of Pub Med, Google scholar, CINAHL, web of science and Scopus. To identify articles related to IUGR, we used the term Fetal IUGR, Doppler study in fetal IUGR, Diagnosis of Fetal IUGR, Aortic flow Doppler in fetal IUGR, MCA flow Doppler in fetal IUGR, UA flow Doppler in fetal IUGR, management of Fetal IUGR were used for identifying variations of these terms. Search was executed after combing the terms related to Fetal IUGR and Doppler study. We included case report as well as case series in our review. We limited the search to English language only. All open access article are reviewed thoroughly. Full



texts of potentially available articles were included to assess for eligibility.

IUGR – Etiopathogenesis

The etiologic basis of IUGR includes maternal as well as fetoplacental factors which are associated with conditions

like chronic hypertension, diabetes mellitus, preeclampsia in early gestation, chronic renal disease, severe hypoxic lung disease, systemic lupus erythematosus, chronic renal disease, maternal infection, drug intake etc. (6).

Table 1: Studies that have been proved abnormal Doppler flow pattern in umbilical artery (UA)/ aortic isthmus (Aol)/ middle cerebral artery (MCA)/ internal carotid artery (ICA)/ Descending aorta (Desc. Ao) among IUGR with some exploring its impact on neonates and children.

Author (year)	Number	Study Design	Included arterial vessel for Doppler assessment	Primary Outcome variable	Perinatal outcome	Results	Comments
F. FIGUERAS (2009)	46	Prospective Cohort	UA/MCA/Aol	Aol Doppler flow	-	In preterm growth restricted fetuses, Aol blood flow becomes abnormal on average 1 week before DV blood flow does	Study did not convey the options for mode and timing of delivery in IUGR w.r.t outcome variable
Domenico Arduini et al (1987)	75	Prospective cohort	UA/ Desc. Ao/ ICA	Desc Ao/ UA PI	-	In the fetus with IUGR, UA/Desc. Ao showed higher PI	This study emphasised on prediction of IUGR by Doppler parameters rather correlation of Doppler parameters with fetal outcome
K. HECHER, et al (2001)	110	Prospective longitudinal multicenter study	UA/ MCA/ DUCTUS VENOSUS	Ductus venous PI	Studied with respect to delivery </>32 weeks of gestation with IUGR	Ductus venous pulsatility index and short-term Variation of fetal heart rate is important indicators for the optimal timing of delivery before 32 weeks of gestation. Delivery should be considered if one of these parameters becomes persistently abnormal.	The study highlighted the importance of ductus venous pulsatility index on close follow up in IUGR cases in determining the timing of delivery.
BN LAKHKAR et al (2006)	58	Prospective singleton study	MCA/Desc. Ao/ UA	S/D ratio of MCA/UA	S/D ratio of MCA/UA is the most sensitive and specific index in predicting major perinatal adverse outcome (83% and 75%), while umbilical artery S/D ratio is the most sensitive index (66.6%) in predicting any adverse perinatal outcome i.e. including both major and minor outcome.	Doppler studies of multiple vessels in the fetoplacental circulation can help in the monitoring of compromised fetus and can help us predicting neonatal morbidity. This may be helpful in determining the optimal time of delivery in Complicated pregnancies.	Although arterial Doppler in antenatal scan would predict adverse perinatal outcome the study limits evidence for isolated IUGR cases.
RIZA MADAZLI et al (2001)	100	Prospective	UA/MCA/Thoracic aorta	UA diastolic flow/ UA PI	Fetal asphyxia producing perinatal mortality could be predicted by absent end diastolic velocity in the umbilical artery. Detection of AEDV in the thoracic aorta was found to be the most significant predictive factor of perinatal deaths	The degree of abnormality found in Doppler findings parallels the severity of fetal compromise in IUGR. Fetuses with AEDV detected both in the umbilical artery and The thoracic aorta is found to be severely compromised with ineffective time gain in utero.	Study confessed that the degree of abnormality found in Doppler parameter would reflect the severity of fetal compromise, thus enhancing the close monitoring and early delivery.

H. M Tonge et al (1986)	12 IUGR 72 normal	Case-control	Desc. Ao	Pulsatile index/ Flow velocity	Reduced peak velocity lesser than 50-55cm/sec preceded abnormal fetal heart rate pattern	Elevated pulsatile index and reduced end-diastolic velocity associated with IUGR whereas this did not correlate with the degree of IUGR severity.	The sample size may not be sufficient for the conclusion.
Irene A.L. Groenenberg ,(1989)	50	Case-control	Cardiac and peripheral	Cardiac velocities	-	In IUGR the reduction in peak systolic flow velocities at a cardiac level may be secondary to either raised after load/reduced flow volume or increased valve/ vessel size.	The study could not discriminate the characteristic changes in the vessel w.r.t altered load and vessel size among IUGR
Jean-Claude Fouron et al (2004)	48	Prospective cohort	AI	IFI	Cut off value for Isthmus flow index of 0.70 was found to be associated with overall positive and negative predictive value for neuro- developmental status. Whereas PI in UA did not possess any explanation for outcome	Isthmic flow index can determine the fetuses with insufficiency in placental circulation which might benefit from early delivery	This supports need for early delivery in IUGR in the presence of altered isthmus flow index
M Del Rio et al (2008)	51	Prospective cross-sectional study	AI/UA	PI and resistance index) / absolute velocities (peak systolic (PSV)	Reversal flow in aortic isthmus strongly correlates with adverse perinatal outcome in IUGR, whereas absolute isthmus velocities found to reduce among these cases.	Doppler holds better role in clinical surveillance in cases with severe IUGR	Imaging aortic isthmus flow pattern would help to predict adverse perinatal outcome in IUGR
E. TIDEMAN et al (2007)	42	Perspective: Divided into 2 cohort study	UA	UA	Executive Cognitive function as assessed by WAISIII was found to be significantly impaired among IUGR subjects at 18 years of age when compared with that of AGA group at 18 years. However, the psychological distress was not potent among IUGR subjects.	Abnormal fetal blood flow in IUGR assessed during fetal life associated with executive cognitive function impairment in young adults.	This study enhances the importance of Doppler study in IUGR for the prediction of impaired executive cognitive function in young adults, requiring close supervised monitoring of IUGR cases even after the delivery.

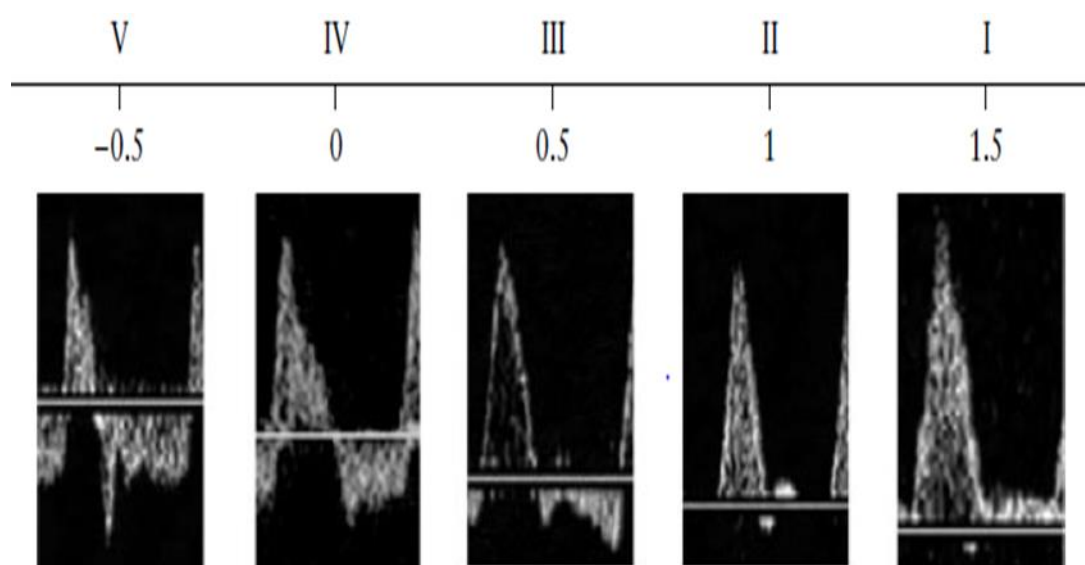


Figure 1: Demonstrates the five possible types (I-V) of isthmus flow pattern in different condition. (Courtesy: J.-C. FOURON by permission)

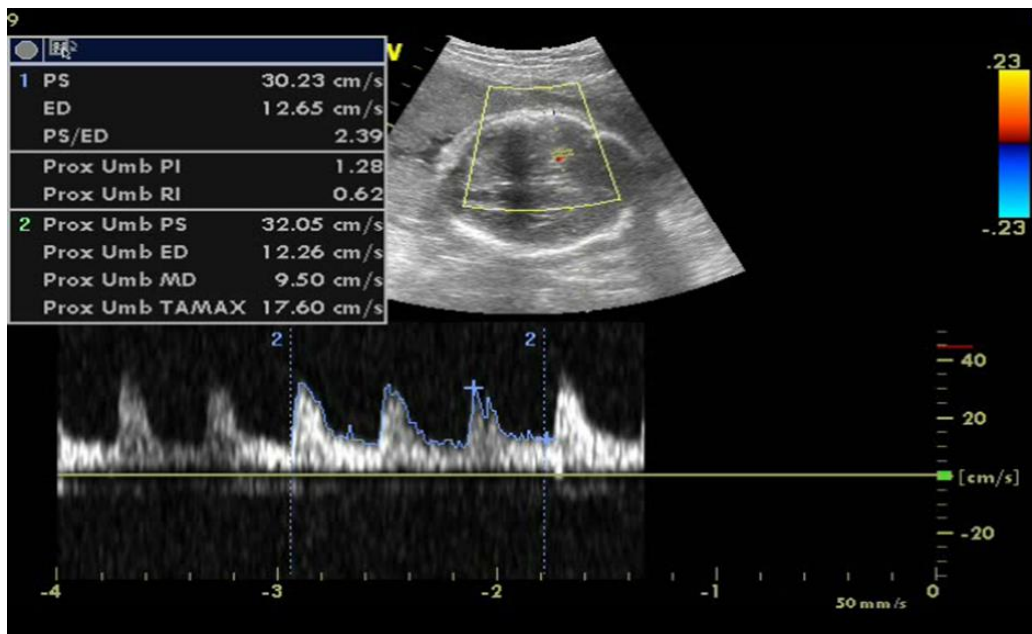


Figure 2: MCA flows showing brain sparing effect: Decreased pulsatile index and increased end diastolic flow.

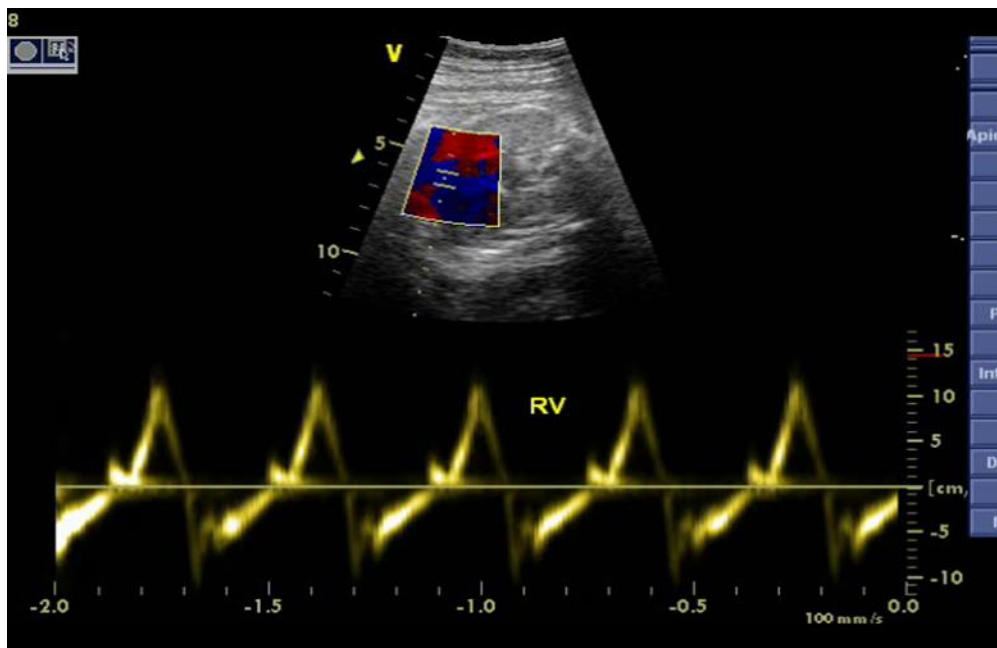


Figure 3: Showing annular tissue velocity pattern in fetus

Normal fetal circulation

Umbilical vein carries oxygenated blood from placenta towards right atrium via ductus venosus / sinusoids in the hepatic channel and is distributed to left atrium through foramen ovale and right ventricle through the tricuspid valve. This oxygenated blood from the left ventricle will be pumped out into pre-ductal aorta enhancing nutrient rich blood flow into myocardium and brain. The right ventricle receives a major source of venous blood from superior vena cava (SVC), and part of inferior vena cava (IVC) flow continuing the stream of flow into the pulmonary artery. Though the pulmonary circulation is by 15% of RV output, the remaining volume is ejected to downstream via ductus arteriosus. Hence the blood flow

across aortic isthmus is determined by the biventricular performance and impedance in the descending aorta/umbilical artery. Normally forward flow via isthmus is noted both in systole and diastole as a result of lesser downstream impedance. This forward flow progressively decreases over a period as the gestation progresses due to right ventricular predominance late in the 2nd half of gestation. The altered isthmus flow pattern also affected by characterization in the changes occurring in cerebrovascular resistance and placental resistance. Cerebrovascular resistance peaks at mid-gestation forming a curvilinear pattern with a progressive decline at the end (7). Whereas at the end of gestation vascular resistance in placenta tends to reach a plateau.

The aortic isthmus flow have been monitored objectively by obtaining the isthmic flow index (IFI) which reflect ratio of total systolic (S) and diastolic (D) flow velocity integral to systolic(S) flow velocity integral, by including positive or negative sign with respect to vector direction of flow, i.e. $IFI=(S+D)/S$. Based on the IFI obtained by Doppler velocity tracking, this can be classified into five different types where $IFI>1$ denotes normal pattern defining the presence of adequate flow both in systole and diastole. IFI can show the value of 1 when the diastolic component is absent, which corresponds to type II. IFI vale between 0 and 1 reveals some amount of flow reversal without competing with Antegrade flow, whereas IFI equal to zero suggest equal antegrade and retrograde flow and classified as type IV. In type V the index shows negative value, less than zero, meaning that the net flow across isthmus is retrograde (7,8).

Doppler abnormality in IUGR shows a significant decrease in diastolic forward flow, and in cases with more severe IUGR may possess diastolic flow reversal as assessed by isthmus Doppler (9,10).

Since middle cerebral artery (MCA) possess lower resistance throughout the pregnancy, it is thought that this could alter early in gestation once IUGR sets in (11, 12), Hence decreased MCA pulsatile index and increase in diastolic flow are peculiar with the mechanism for sparing cerebral flow. In IUGR compensatory mechanism sets in the form of decreased MCA pulsatile index with increased diastolic flow component, which favourably redistributes the flow toward important vital organs like heart, brain and kidney. However, the continued hypoxic exposure will result in failure of brain sparing effect with restoring normal diastolic flow return, which denotes its decompensation state of the fetus. Further, it deteriorates into brain edema, where the diastolic flow reversal may exist due to raised intracranial pressure which is associated with irreversible fetal adverse neurological outcome (13-15).

Umbilical artery is one of the important vessels that reflects changes in placental circulation, in the setting of IUGR, it is found that absent/reversed diastolic flow is associated with higher incidence of the perinatal adverse outcome (16). The perinatal death of approximate 40 % prevalence is associated with pre-detected absent or reversed end diastolic flow, with AEDF being the strong independent predictor of perinatal adverse outcome (17).

Effect of IUGR on heart

It is also evident that myocardial function impairment may precede or follow IUGR. Whereas fetal heart programming in IUGR plays an important regimen for the persisting subtle myocardial abnormality. Recently the studies have shown the uses of tissue Doppler imaging (TDI) technique over conventional methods of assessing myocardial function. TDI in fetus enhances assessment of both systolic and diastolic function assessment with nullifying the effect of preload on the heart as compared

to conventional method. It is shown that altered myocardial performance can interfere with normal peripheral vessel flow pattern (18-20).

Management

Management in IUGR mainly aims the time course at which the subject has to deliver. In literature, data is limited for the Doppler based decision on the timing of delivery. Studies have shown the treatment choice based on subjects biophysical property (BPP). It is found that cesarean delivery for IUGR fetus may be considered in the setting of absent/ flow reversal in umbilical artery since this fetus rarely tolerates vaginal delivery attempts irrespective of BPP value (21).

CONCLUSION

1. Based on the systematic review non-invasive Doppler ultrasound method is a novel method for prediction of IUGR.
2. In the review, the evidence is not established as few studies have not compared the gold standard as MCA.
3. A review highlights that periodic Doppler assessment in IUGR has the effective tool in assessing the hemodynamic state of the fetus and abnormal patterns that predict the adverse perinatal outcome. This engages the IUGR subjects in close monitoring and helps in minimising perinatal complications.

Limitations

1. **Sample size calculation:** None of the above-discussed studies disclosed the sample size evaluation method
2. Since the Doppler assessment has to be corrected for the gestational age for interpretation, the guiding criteria for the timing of delivery do not exist, however, these parameters give indirect evidence on perinatal outcome. Once the abnormal Doppler indices detected then the close follow-up of the subject with adjunct therapy would help the population for better outcome
3. Other than the english language, we have not included in the literature review.

Recommendation

Based on the literature, the prevalence of IUGR in India is increasing. However, there is no study published in Indian population. Therefore our review highlights the need for screening, diagnosis and appropriate management during the pregnancy.

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