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Original Research Article

Myocardial Tissue Doppler in Intrauterine Growth Restriction

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Abstract

Objective: A recently postulated method to detect function of the myocardium is the use of Tissue Doppler Echocardiography. As in IUGR, subclinical cardiac dysfunction may set in before the development of ultrasonically visible changes in the foetal circulation; the technique may be able to detect growth restriction changes earlier than conventional vessel Doppler. We undertook this study to assess whether myocardial tissue Doppler is an effective tool in detecting foetal cardiac changes in Intrauterine growth restriction.

Materials and Methods: Fetuses in the third trimester of gestation (28-40 weeks) were taken for this prospective case control study. Myocardial Tissue Doppler was used to assess their foetal cardiac function. E', A, E'/A' and Myocardial performance index (MPI') of both ventricles and the interventricular septum were compared between the two groups of IUGR and normal growth fetuses among the study subjects. Comparison was also done after further classifying the IUGR group based on their birth weight, vessel Doppler inferences and outcomes in the neonatal period.

Results: Among the 63 patients taken for the study, thirty-three were found to have IUGR and thirty were of normal growth fetuses. In fetuses with IUGR, there was a significant difference in the interventricular septal variables in comparison to their normal counterparts. In fetuses with birth weight between 1-1.5 kg, the right ventricle and left ventricle parameters were also found to be affected. The parameters showed no remarkable deviation in the IUGR fetuses with respect to vessel Doppler and fetal outcomes.

Conclusion: We conclude that Myocardial tissue Doppler can diagnose cardiac dysfunction in IUGR. This change was more significant in babies with very low birth weight, abnormal vessel Doppler and adverse perinatal outcomes. Myocardial tissue Doppler has, however, a low specificity in predicting adverse perinatal outcomes in IUGR babies and comparable sensitivity to Conventional Vessel Doppler.

Keywords: Myocardial tissue Doppler, Cardiac dysfunction, IUGR, Birth weight, outcomes

Introduction

Karl Issaz first described Tissue Doppler as an investigative modality in 1989 [1]. The technique of Myocardial tissue Doppler ultrasonography constitutes the measurement of velocity of the myocardium in both systole and diastole. This establishes its superiority over conventional echocardiography where the transvalvular mitral and tricuspid blood flow analysis gets influenced by a high cardiac rate and after load conditions. In adults and children, TDI (tissue Doppler imaging) has been demonstrated to be useful in prediction of future cardiovascular diseases.

Doppler insonation of the heart generates signals both from cardiac blood flow and myocardial movement. The signals generated by the blood flow are of lower amplitude and higher frequency than those from myocardial movement. Tissue Doppler Echocardiography filters out the high frequency blood flow signals to accurately look at the tissue function [2].

That the placental dysfunction associated with Intrauterine growth restriction has pathological consequences on the fetal heart has been proven in several studies [3-6]. Myocardial Contractility, developmental maturation as well as loading conditions are some of the various factors that determine the complex fetal cardiac function. In conditions jeopardising the fetus, notable among them being intrauterine growth restriction, cardiovascular dysfunction appears.

In the initial stages of the condition, the fetal Cardiovascular system tries to adapt by preferentially shifting the majority of the cardiac output towards the brain. There is hence cerebral vasodilatation with resultant decrease in the left ventricular afterload and systemic and pulmonary vasoconstriction leading to an increment in the right ventricular afterload. As the placental dysfunction worsens, the consequent progressive hypoxia causes inevitable breakdown of this mechanism leading to improper cardiac filling and fall in cardiac function [7,8].

Just as in adults and children, the procedure of Myocardial tissue Doppler has been reported to be feasible in fetuses also [9-11]. Fetuses tend to be far ahead in the spectrum of cardiovascular deterioration by the time before the signs of fetal distress appear on biophysical tests, so investigative modalities that can detect the earliest signs will be a great help in the management of fetuses afflicted with growth restriction. Myocardial tissue Doppler in this regard has been found quite sensitive in predicting the initial changes in cardiovascular system in fetuses with IUGR [12-14]. Our study tries to explore if Myocardial tissue Doppler can detect cardiac dysfunction in IUGR fetuses and do variations of vessel Doppler, birth weight or neonatal outcomes have any effect on its findings.

Materials and Methods

We conducted a prospective observational case control study in a tertiary care hospital for a period of three years. The study subjects were Mothers in the third trimester of gestation. Patients were explained about the study and written consent was taken from all of them. Two groups were formed among them:

Study Group: Patients identified by ultrasound with fetuses having IUGR-defined as growth curve below the 10th percentile for their gestational age [15].

Control Group: Patients with fetuses with growth matching their gestational age.

Fetuses with diagnosed cardiac anomalies and those in multiple pregnancies were excluded from the study as it is difficult to perform the technique on them.

Vivid GE machine was used to perform fetal echocardiography along with myocardial tissue Doppler in all the study subjects. The standard areas of fetal echocardiography i.e., the interventricular septum and the basal part of the free wall of both ventricles were taken for making the measurements.

The variables of tissue Doppler which were used for this study were [16]:

E'- average velocity of three measured early diastolic waves, A'-the average velocity of three measured late diastolic waves, E'/A'- Their ratio,

Myocardial performance index (MPI') - Also known as Global Cardiac index denoted by ICT'+IRT'/ET' where ICT' is isovolumetric contraction time, ET' ejection time and IRT' isovolumetric relaxation time.

Conventional vessel Doppler was done on all the subjects at the level of the umbilical artery, middle cerebral artery and ductus venosus. All of them were followed up to 7 days post-delivery. NICU admission for > 5 days, hypoglycemia, respiratory distress syndrome, presence of cardiomegaly, neonatal seizures and mortality were regarded as adverse neonatal outcomes for the study.

Independent t test was used to make the comparison of the inferences of myocardial tissue Doppler between the study and control group. This analysis was further done after dividing the study subjects into groups depending upon their vessel Doppler findings, birth weight and neonatal outcomes. The findings of the study were computed with the help of SPSS software 16.

Results

Among the 63 study subjects taken, thirty-three patients were diagnosed to have fetuses with IUGR and Thirty with normal growth.

The fetuses with IUGR were further classified based on their birth weight:

A-(Birth weight < 1 kg)-3 in present study
B-(Birth weight 1-1.5 kg)-5 in present study
C -(Birthweight 1.5 -2 kg)-11 in present study
D-(Birth weight-2-2.5 kg)-14 in present study

None of the fetuses within the normal growth group were found to have abnormal findings with Doppler. Among the fetuses with IUGR, eleven had abnormal vessel Doppler (Raised umbilical artery indices or absent or reversed end diastolic flow) while twenty-two had normal findings. Myocardial tissue Doppler was performed on all these fetuses and its efficacy in detecting cardiac dysfunction was assessed.

Demographic factors of the two groups had no statistically significant difference except for preeclampsia which is known to be more frequently associated with Intrauterine growth restriction [17] (Table 1). The average gestational age of performing the test was 33.1+/-0.41 weeks in IUGR fetuses and 34.1+/-0.44 weeks in Normal growth fetuses. No statistically significant difference between them rules out gestational age as a confounding factor.

Table 1: Demographic attributes of the patients taken for the study

	IUGR/Normal growth				p-value	
	IUGR (33)		Normal growth (30)			
	Mean	SD	Mean	SD		
Age in years	28.10	4.74	27.22	3.70	0.974	
		N	%	N	%	
Parity	primi	17	53.2%	15	50%	0.901
	Multiple abortions	5	14.5%	4	13.7%	
	multi	11	32.3%	11	36.3%	
Dating	excellent	23	70.9%	19	62%	0.111
	good	8	25.8%	7	24.1%	
	poor	2	3.3%	4	13.9%	
Preeclampsia	yes	9	27.4%	0	0%	0.00
	No	24	72.6%	30	100%	

Chi square test used, significant p Value <0.05

On comparison of the Myocardial tissue Doppler parameters of the two groups of IUGR and normal growth fetuses (Table 2), only the interventricular septal E' and E'/A' of the study fetuses were found to be significantly lesser than those of control fetuses.

Table 2: Myocardial tissue Doppler parameters of IUGR and normal growth fetuses:

	Normal growth/IUGR				p-value
	IUGR(N-33)		Normal growth(N-30)		
	Mean	SD	Mean	SD	
IV-E'	.03	0.01	.04	0.01	**0.036**
IV-A'	.05	0.01	.05	0.02	0.49
IV-E'/A'	0.75	0.25	0.97	0.36	**0.012**
IV-MPI'	0.65	0.08	0.65	0.09	0.922
LV-E'	0.06	0.05	0.05	0.01	0.396
LV-A'	0.07	0.03	0.07	0.02	0.84
LV-E'/A'	0.77	0.39	0.83	0.23	0.46
LV-MPI'	0.63	0.16	0.65	0.12	0.60
RV-E'	0.08	0.013	0.07	0.02	0.47
RV-A'	0.09	0.02	0.10	0.02	0.23
RV-E'/A'	0.60	0.23	0.70	0.19	0.10
RV-MPI'	0.67	0.19	0.68	0.12	0.66

Independent t test used, p value <0.05significant. E', A' are in m/sec, E'/A' and MPI' ratios.

To look for correlation of Myocardial tissue Doppler with birth weight, the IUGR fetuses were classified based on their birth weight and their parameters compared (Table 3). In fetuses with birth weight between 2-2.5 kg, not only the interventricular E'/A' but also that of the left ventricle came across significantly lower than normal growth fetuses. The same situation persisted in fetuses with birth weight between 1.5-2 kg. In fetuses with birth weight between 1-1.5 kg however, it was the right ventricular E'/A' and MPI' which were found to be significantly lower instead of interventricular septum.

Table 3: Comparison of Myocardial tissue Doppler parameters based on birth weight

			p-value
	A (Birth weight<1 kg) (N-3)	**Normal (N-30)**	
	Mean±SD	Mean±SD	
RV-E'	0.06±0.01	0.07±0.01	0.62
RV-A'	0.08±0.01	0.09±0.03	0.61
RV-E'/A'	0.69±0.10	0.72±0.21	0.87
RV-MPI'	0.47±0.04	0.72±0.14	**0.04**
	B (Birth weight 1-1.5 kg) (N-5)	Normal (N-30)	
LV-E'/A'	0.84±0.16	0.87±0.22	**0.01**
RV-E'/A'	0.43±0.07	0.72±0.21	**0.02**
RV-MPI'	0.49±0.23	0.72±0.14	**0.04**
	C (Birth weight 1.5-2 kg) (N-11)	Normal (N-30)	
IV-E'/A'	0.60±0.20	0.97±0.44	**0.03**
LV-E'/A'	0.59±0.22	0.87±0.22	**0.01**
	D (Birth weight 2-2.5kg) (N-14)	Normal (N-30)	
IV-E'/A'	0.60±0.20	0.97±0.44	**0.03**
LV-E'/A'	0.59±0.22	0.87±0.22	**0.01**

Independent t test used, p value <0.05 significant.

When Myocardial tissue Doppler parameters were compared between IUGR fetuses with abnormal vessel Doppler (11 in the present study) and those with normal growth, Interventricular and left ventricular E'/A' were found significantly lower in alignment with our previous findings (Table 4).

Table 4: Comparison of Myocardial tissue Doppler in fetuses with IUGR and abnormal Vessel Doppler and normal growth fetuses

	IUGR		**p-value**
	Abnormal Doppler (N-11)	**Normal Growth (N-30)**	
	Mean±SD	Mean±SD	
IV-E'	0.037±0.009	0.040±0.011	0.13
IV-A'	0.04±0.13	0.05±0.014	0.50
IV-E'/A'	0.66±0.24	0.95±0.36	**0.02**
IV-MPI'	0.60±0.10	0.61±0.10	0.66
LV-E'	0.053±0.017	0.051±0.012	0.71
LV-A'	0.06±0.026	0.07±0.021	0.61
LV-E'/A'	0.58±0.40	0.82±0.23	**0.02**
LV-MPI'	0.62±0.17	0.65±0.11	0.47
RV-E'	0.063±0.011	0.062±0.01	0.77
RV-A'	0.09±0.02	0.10±0.02	**0.05**
RV-E'/A'	0.64±0.15	0.62±0.26	0.73
RV-MPI'	0.58±0.18	0.69±0.12	0.83

Independent t test used, p value <0.05 significant. E', A' in m/sec, E'/A' and MPI' are ratios.

On comparing the parameters of the two groups of IUGR fetuses formed based on conventional vessel Doppler with each other, no significant differences were found in the tissue Doppler variables (Table 5).

Table 5: Comparison of Myocardial tissue Doppler parameters among IUGR fetuses based on conventional Vessel Doppler:

	IUGR		p-value
	Abnormal Doppler(N-11)	Normal Doppler (N-22)	
	Mean±SD	Mean±SD	
IV-E'	0.03±0.001	0.03±0.01	0.27
IV-A'	0.0481±0.13	0.486±0.11	0.88
IV-E'/A'	0.79±0.37	0.84±0.26	0.56
IV-MPI'	0.60±0.10	0.63±0.08	0.27
LV-E'	0.05±0.02	0.06±0.05	0.52
LV-A'	0.068±0.02	0.061±0.02	0.23
LV-E'/A'	0.76±0.37	0.92±0.32	0.08
LV-MPI'	0.62±0.17	0.64±0.09	0.68
RV-E'	0.06±0.01	0.08±0.11	0.37
RV-A'	0.09±0.02	0.094±0.02	0.50
RV-E'/A'	0.64±0.15	0.62±0.22	0.74
RV-MPI'	0.58±0.18	0.69±0.12	0.10

Test used: Independent t test, p value <0.05 significant.

The subjects of the study were all followed up to a week post-delivery. Twenty-one IUGR babies required NICU admission of more than 5 days. Twelve out of them had severe complications of respiratory distress requiring ventilator care. Hypoglycemia or cardiomegaly was not seen in any of these babies. There were no mortalities. In the group of fetuses with normal growth, none of the babies had NICU admission for any adverse outcome.

In the 21 IUGR babies with adverse outcomes, 10 were found to have abnormal vessel Doppler. These babies also had lower myocardial tissue Doppler parameters than normal babies. In the twelve babies with normal outcomes, only one baby had abnormal vessel Doppler values while five had abnormal tissue Doppler values.

Also, when the myocardial tissue Doppler parameters were compared between IUGR babies with abnormal vessel Doppler and adverse outcomes with the ones with normal vessel Doppler and outcome, no remarkable difference was found (Table 6).

Table 6. Comparison of Myocardial tissue parameters among IUGR babies with adverse neonatal outcomes based on their vessel Doppler records:

	IUGR with adverse outcomes(N-21)		p-value
	Abnormal Doppler (N-10)	Normal Doppler (N-11)	
	Mean±SD	Mean±SD	
IV-E'	0.03±0.01	0.03±0.01	0.73
IV-A'	0.05±0.13	0.49±0.13	0.64
IV-E'/A'	0.81±0.33	0.85±0.30	0.52
IV-MPI'	0.61±0.10	0.62±0.09	0.68
LV-E'	0.05±0.02	0.07±0.01	0.47
LV-A'	0.066±0.023	0.068±0.022	0.73
LV-E'/A'	0.80±0.36	0.80±0.28	0.99
LV-MPI'	0.628±0.17	0.647±0.11	0.59
RV-E'	0.06±0.01	0.07±0.007	0.56
RV-A'	0.09±0.017	0.09±0.02	0.14
RV-E'/A'	0.63±0.15	0.62±0.24	0.93
RV-MPI'	0.61±0.26	0.66±0.14	0.64

p value <0.05 is significant. E’, A’ in m/sec, E’/A’ and MPI’ are ratios.

Discussion

It was a prospective case control study carried out to assess if Myocardial tissue Doppler can detect early cardiac dysfunction and predict adverse perinatal outcome in IUGR. Sixty-three patients were taken among which thirty-three were IUGR and thirty were fetuses with normal growth. Myocardial tissue Doppler analyses the high amplitude and low frequency signals generated by the myocardial tissue while movement during the cardiac cycle irrespective of how the loading conditions are [2]. This assists in differentiating actual cardiac dysfunction from compensatory altered functioning to tide over disadvantageous circulatory changes.

A diagnosis of IUGR can hardly be made with proper certainty without proper dating. All of our patients had excellent or good dating, leaving slim chances of a false categorization. Inter observer variations and biases arising due to expertise and knowledge were taken care of by carrying out all measurements on the same machine and by the same trained person. Our comparison of the myocardial tissue Doppler parameters between fetuses with IUGR and normal growth, yielded mostly lower values in the former groups. This is indicative of total reduction in efficacious cardiac function in IUGR. The parameters significantly reduced were those of Interventricular septum. This finding of the study shows that the interventricular septum is the area most prone to be affected with the increasing hypoxia of the placental insufficiency. With the advancing dysfunction, either there has been a decrease in the magnitude of the early diastolic waves or there is a compensatory increase in the atrial velocity as seen in the late diastolic waves causing a reduction in their overall ratio.

It can be argued that increasing volume and size of the cardiac tissue with gestational age can affect cardiac tissue function and hence tissue Doppler findings. Chan *et al* demonstrated in their study that E' was found to increase progressively with gestational age [18]. The late diastolic waves velocity also showed a similar surge but of a smaller magnitude. However, this study has taken fetuses in both second and third trimester. Our study was confined only to fetuses in the third trimester. Matching was done for the gestational age for each subject in the study with the control group. Also, we did not find any correlation of the myocardial tissue velocities from 28-40 weeks of gestation. The myocardial velocities were similar for all fetuses across their gestational ages in both the groups.

Like all IUGR fetuses combined, most of the parameters were lower than the normal growth fetuses when compared separately based on their birth weight. The parameters of Myocardial tissue Doppler were found to be affected differently with increase in the severity of the pathologic process of IUGR which was reflected in the birth weight. In fetuses with birth weight between 1.5-2.5 kg, the interventricular and left ventricular E'/A' were significantly lower than normal growth babies. In fetuses with birth weight between 1and 1.5 kg, the right ventricular E'/A' and MPI' are also affected in addition to the left ventricle while in those <1 kg, significant decrease is only confined to the right ventricular MPI'.

From these findings, we surmise the interventricular septum is the area most prone for hypoxia with the development of ischemia of the circulatory changes of IUGR. With persistent circulatory changes which have prevented the fetuses from growing beyond 2 kg the situation has extended to first the left and then the right ventricle.

In fetuses with birth weight <1 kg the Right Global Cardiac Index was noteworthy. Right side of the heart is dominant over the left in fetuses [18]. It suffices to say hence it would be the portion requiring more of oxygen and nutrients and not very adaptable to their deficiency. This is a possible explanation for finding the right sided parameters abnormal in fetuses with pathologic growth restriction causing their weight to decrease drastically and condition to deteriorate leading to their premature delivery.

Why the interventricular septum variables are found not significantly decreased in fetuses of less than 1 kg could be explained by adaptation at the cellular and molecular level in view of prolonged exposure to the circulatory changes to tide over the crisis. When the process of insufficiency worsened beyond the realm of compensation leading to very severe IUGR, the cardiac function has worsened as observed by a decrease of the Right MPI', a marker of global cardiac function. The right ventricular ejection time has prolonged or there is a decrease in the isovolumetric contraction or relaxation time. The right ventricle being the most active component of the fetal heart is unable to adapt sufficiently unlike the others and hence is the only area to be found affected in very severe IUGR [18]. The inferences of our study are comparable to the findings of a similar study undertaken by Naujorks *et al*

[12]. Naujorks *et al* in another recent study done on the same lines also found a lower mobility at the level of the septum primum indicating a raised left atrial pressure along with raised Septal E'/A' values in IUGR [20]. However, the sample size was much low and only fetuses above 30 weeks were taken which could explain the different findings from our study.

Our present study differs from most of the present literature with the finding of lower MPI' in IUGR fetuses in comparison to those with normal growth. Most studies concluded a higher value of global cardiac index in IUGR fetuses. The authors explained this as decreased stiffness of myocardial tissue in normal growth babies that doesn't occur in IUGR babies with increasing gestational age [12-14,20-22]. This variation of our study could be due to the difference of genetic and ethnic factors of the study populations. Another reason could be the other studies have taken more severely growth restricted fetuses and our finding could be an early adaptive change of decreased contraction and relaxation time or a prolonged ejection time with the beginning of placental dysfunction, slowly progressing on to the prevalent observation of increased MPI' with saturation of these mechanisms.

We had 22 IUGR fetuses with normal vessel Doppler out of which Eleven still had adverse neonatal outcomes. In the present study, it was found that the IUGR fetuses with abnormal vessel Doppler showed significant reduction in Interventricular Septal and left ventricular E'/A' than normal growth fetuses. But comparison of the 11 IUGR fetuses with normal Doppler showed no significant difference. This finding denotes that a majority of the abnormalities of myocardial tissue Doppler seen in IUGR are only confined to the fetuses also with abnormal Vessel Doppler.

Despite indicating the presence of cardiac dysfunction in IUGR fetuses, the myocardial tissue Doppler parameters fared poorly in specificity in predicting the fetuses with increased chances of developing adverse neonatal outcomes. Cutoff levels to define abnormal Myocardial Tissue Doppler have still not been defined on account of the research still in the nascent phase. But in the babies with adverse outcomes in our study, twelve were found to have significantly lower myocardial tissue Doppler values. However, there were five out of 12 IUGR babies with normal neonatal outcomes who still had statistically lower myocardial tissue Doppler than normal growth fetuses.

Despite this observation, we must not forget the long-term effects of IUGR on cardiac function. These findings may be indicative of a latent cardiac dysfunction with manifestations in the future.This can be stated definitely however, if these babies could be followed up long term which was not done.

As per the observations, Myocardial tissue Doppler can predict cardiac dysfunction in IUGR and has a good sensitivity in diagnosing its overt manifestation in the fetuses. But as seen on comparison with different birth weight babies, a definite parameter for making such predictions couldn't be decided upon. We need more research with a bigger sample size to determine its usefulness in the management of Intrauterine growth restriction.

30% of the mothers with IUGR fetuses taken for the study also had preeclampsia in addition. Even though preeclampsia is a major cause and adjunct condition with IUGR [16], some of the findings may have been affected by its presence. Also not many IUGR fetuses with birth weight <1kg could be included in the study. This was because many such cases were referred with fetal compromise leaving no time to conduct the test on them. Also, Troponin T levels of these fetuses could not be done to correlate our inferences with actual myocardial damage.

We conducted this to determine if the latest technique of Myocardial tissue Doppler could replicate its success among adults and children in fetuses as well. Our inferences show significant differences in some parameters in the IUGR group. But trying to correlate these findings with conventional vessel Doppler and perinatal outcomes did not yield very good results. Myocardial tissue Doppler parameters had low specificity in detecting adverse outcomes in the IUGR fetuses as well as slightly lower sensitivity than conventional vessel Doppler for this purpose.

Conclusion

We conclude that Cardiac dysfunction in IUGR can be detected by Myocardial Tissue Doppler. This change was more significant in babies with very low birth weight, abnormal vessel Doppler and adverse perinatal outcomes. Myocardial tissue Doppler has, however, a low specificity in predicting adverse perinatal outcomes in IUGR babies and comparable sensitivity to Conventional Vessel Doppler. Further research is needed before deciding it as a diagnostic tool in the treatment of fetuses affected with IUGR.

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References

1. Isaaz K, Thompson A, Ethevenot G, Cloez JL, Brembilla B, Pernot C. Doppler echocardiographic measurement of low velocity motion of the left ventricular posterior wall. The American Journal of Cardiology. July, 1989; 64 (1): 66–75.
2. Dev Maulik. Introduction to Fetal Doppler Echocardiography. In: Maulik, Doppler Ultrasound in obstetrics and gynecology. 2nd edition. New York. Springer; 2005; 465-482
3. Mäkikallio K, Vuolteenaho O, Jouppila P, Räsänen J. Association of severe placental insufficiency and systemic venous pressure rise in the fetus with increased neonatal cardiac troponin T levels. Am J Obstet Gynecol. 2000; 183: 726-31
4. Acharya G, Räsänen J, Mäkikallio K, Erkinaro T, Kavasmaa T, Haapsamo M, Mertens L, Huhta JC. Metabolic acidosis decreases fetal myocardial isovolumic velocities in a chronic sheep model of increased placental vascular resistance. Am J Physiol Heart Circ Physiol. 2008; 294:498-504
5. Crispi F, Hernandez-Andrade E, Pelsers MM, Plasencia W, Benavides-Serralde JA, Eixarch E, Le Noble F, Ahmed A, Glatz JF, Nicolaides KH, Gratacos E: Dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. Am J Obstet Gynecol. 2008; 199:254
6. Mäkikallio K, Vuolteenaho O, Jouppila P, Räsänen J. Ultrasonographic and biochemical markers of human fetal cardiac dysfunction in placental insufficiency. Circulation. 2002 30; 105:58-63.
7. Bahtiyar MO, Copel JA. Cardiac changes in the intrauterine growth-restricted fetus. SeminPerinatol. 2008; 32:190-3.
8. Ahm*et al*exander Baschat. Intrauterine growth restriction. In: James D, Steer P, Weiner C, Gonik B, editors. High Risk Pregnancy Management Options.4th edition. New York. Elsevier; 2011; 173-196
9. Harada K, Tsuda A, Orino T, Tanaka T, Takada G. Tissue Doppler imaging in the normal fetus. Int J Cardiol. 1999; 71(3): 227-34.
10. Paladini D, Lamberti A, Teodoro A, Arienzo M, Tartaglione A, Martinelli P.

Tissue Doppler imaging of the fetal heart. UltrasoundObstet Gynecol. 2000; 16(6): 530-5.
11. Tutschek B, Zimmermann T, Buck T, Bender HG. Fetal tissue Doppler echocardiography: detection rates of cardiac structures and quantitative assessment of the fetal heart. Ultrasound Obstet Gynecol. 2003;21(1):26-32
12. Naujorks AA, Zielinsky P, Beltrame PA, Castagna RC, Petracco R, Busato A, Nicoloso AL, Piccoli A, ManicaJL.Myocardial tissue Doppler assessment of diastolic function in the growth-restricted fetus. Ultrasound Obstet Gynecol. 2009; 34:68-73
13. Comas M, Crispi F, Cruz-Martinez R, *et al*. Usefulness of myocardial tissue Doppler vs. conventional echocardiography in the evaluation of cardiac dysfunction in early-onset intrauterine growth restriction. Am J Obstet Gynecol 2010; 203:451-7
14. Comas M, Crispi F, Cruz-Martinez R, *et al*. Tissue Doppler echocardiographic markers of cardiac dysfunction in small-for-gestational age fetuses. Am J Obstet Gynecol 2011; 205:571-6
15. Peleg D,Kennedy C,Hunter S. Intrauterine growth restriction: Identification and management. Am Fam Physician. 1998 Aug 1;58(2):453-460.
16. Doppler Ultrasound in obstetrics and gynecology. In: Maulik William J Ott, editors. Doppler Ultrasound in the Diagnosis and Management of IUGR. 2nd edition. New York. Springer; 2005. 281-293
17. Ian Donald's Practical Obstetric problems. In: Misra R, Bhatla N, KocharS. editors. Intrauterine growth restriction. 6th edition. New Delhi. B I Publications. 2007: 333-344.
18. Smolich JJ, Berger PJ, Walker AM. Interrelation between ventricular function, myocardial blood flow and oxygen consumption at birth in lambs. Am J Physiol 1996;270:H741–9.
19. Chan LY, Fok WY, Wong JT, Yu CM, Leung TN, Lau TK. Reference charts of gestation-specific tissue Doppler imaging indices of systolic and diastolic functions in the normal fetal heart. Am Heart J. 2005; 150:750-5.
20. Naujorks AA, Zielinsky P, Klein C, Nicoloso LH, Piccoli AL Jr, Becker E, Frajndlich R, Pizzato P, Barbisan C, Busato S, Lopes M. Myocardial velocities, dynamics of the septum primum, and placental dysfunction in fetuses with growth restriction. Congenit Heart Dis. 2014 Mar-Apr;9(2):138-43.
21. Comas M, Crispi F, Cruz-Martinez R, Martinez JM, Figueras F, Gratacós E. Usefulness of myocardial tissue Doppler vs conventional echocardiography in the evaluation of cardiac dysfunction in early-onset intrauterine growth restriction. Am J Obstet Gynecol. 2010 Jul;203(1):45.e1-7.
22. Palalioglu RM, Erbiyik HI, Kaya B, Kiyak H, Gedikbasi A. Investigation of fetal cardiac function using tissue doppler imaging in fetuses compromised by growth restriction. Ginekol Pol. 2021;92(3):195-204.