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Investigating myocardial performance in normal and sick fetuses by abdominal Doppler signal derived indices

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ABSTRACT

Introduction: Fetal myocardial performance indices are applied to assess aspects of systolic and diastolic function in developing fetal heart. The aim of this study was to determine normal values of Tei Index (TI) and modified TI (KI) for systolic and diastolic performance in early (<30 weeks), Mid (30–35 weeks) and late (36–41 weeks) relating to both normal fetuses as well as fetuses carrying a variety of fetal abnormalities, which do not call for precise anatomic imaging.

Material and methods: Fetal Electrocardiogram Signals (FES) and Doppler Ultrasound Signal (DUS) were simultaneously documented from 55 normal and 25 abnormal fetuses with a variety of abnormalities including Congenital Heart Diseases (CHDs) and a variety of non-CHDs. The isovolumic contraction time (ICT), isovolumic relaxation time (IRT), ventricular ejection time (VET) and ventricular filling time (VFT) were estimated from continuous DUS signals by a hybrid of Hidden Markov and Support Vector Machine based automated model. The TI and the KI were calculated by using the formula (ICT + IRT)/VET and (ICT + IRT)/VFT respectively.

Results: The TI was not found to show any significant change from early to late fetuses, nor between normal and abnormal cases. On the other hand, KI was shown to significantly decline in values from early to late normal cases and from normal to abnormal groups. Significant correlation ($r = -0.36$; $p < 0.01$) of gestational ages with only KI (not TI) was found in this study.

Conclusion: Modified TI (KI) may be a useful index to monitor the normal development of fetal myocardial function and identify fetuses with a variety of CHD and non-CHD cases.

1. Introduction

[1]Congenital heart defects (CHD) and fetal distress (e.g., low oxygen levels in fetus) are the most common major causes of congenital abnormalities and intrauterine mortality (Hoffman, 1995). Currently, ultrasonography based Doppler techniques are the gold standard for prenatal CHD diagnosis and management (Velayo et al., 2011). Routine ultrasound at 16–22 weeks can identify 25–60% of major heart defects (Kähler et al., 2002). But the majority of CHD cases are still undetected or detected postnatally and unfortunately most are discovered in low-risk pregnancy populations who are not regularly screened by ultrasound scans. Fetal heart rate (FHR) monitoring is commonly used for monitoring purpose and usually performed by using Cardiotocography (CTG) which is a combination of Doppler ultrasound (DUS) and uterine activity (Marzbanrad et al., 2014). However, sometimes abnormal variability in FHR may not necessarily represent the distressed fetuses (Murphy et al., 1990; Vincent et al., 1991). The systolic time intervals (STI) of the fetal cardiac cycle have been analysed by several authors in the past and

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[1] *Abbreviations*: FES, fetal electrocardiogram signals; DUS, Doppler ultrasound signal; CHD, congenital heart diseases; PEP, The pre-ejection period; ICT, isovolumic contraction time; IRT, isovolumic relaxation time, VET, ventricular ejection time; VFT, ventricular filling time; TI, Tei Index; KI, K-Index; SVM, support vector machine; HMM, hidden Markov model; VSD, ventriculoseptal defect; ASD, atrial septal defect; PA, pulmonary atresia (PA); TOF, tetralogy of Fallot; CD, cardiac dilatation; EA, Ebstain anomaly; SSS, sick sinus syndrome; PAC, premature atrial contraction; AV block, Atrio-ventricular block; IUGR, Intrauterine growth restriction; NIHF, placental abruption/dysfunction, non-immune Hydrops fetalis; HF, immune Hydrops fetalis; FGR, fetal growth restriction; FHR, Fetal heart rate; CTG, Cardiotocography; fECG fetal ECG; Mc, Mitral valve closing; Mo, Mitral valve opening; Ac, Aorta closing; Ao, Aorta opening; fRR, Fetal R-R interval.

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showed differentiation of fetuses with fetal growth restriction (FGR) and other perinatal problems (Organ et al., 1980; Koga et al., 2001; Khandoker et al., 2009). The pre-ejection period (PEP: QRS onset until aortic valve opening) and left ventricular ejection time (VET: time between aortic opening till closing) were reported to be sensitive markers of fetal cardiac performance (Murata et al., 1978). PEP refers to a sensitive indicator of the function state of the fetal myocardium. In case of hypoxemia and acidosis, they become prolonged (Organ et al., 1980). Another study suggested to use isovolumetric contraction time (ICT: mitral valve closure until aortic valve opening) as a reliable index. This index could be substituted for fetal cardiac contractility (Yumoto et al., 2005). Isovolumic relaxation time (IRT: aortic valve closure until mitral valve opening) measures ventricular relaxation which also correlates with invasive indices (Myreng and Smiseth, 1990). Prolongation of the IRT accurately categorized fetuses with FGR and abnormal placental function up to 8 weeks prior to abnormalities detected by conventional Doppler hemodynamic indices (Tsyvian et al., 2008). Fetuses with Hb Bart's disease were reported to have reduced ventricular filling time (VFT) (Chao et al., 2009).

Myocardial Performance Index reported by Tei (1995) was proposed to be a combined index of systolic and diastolic cardiac function because Tei Index (TI) [i.e. (ICT + IRT)/VET] is defined as the sum of the isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ventricular ejection time (VET) for each ventricle. TI was used in assessing fetal myocardial performance in sick fetuses by Pulsed Doppler fetal echocardiography (Chao et al., 2009; Ichizuka et al., 2005). A higher myocardial performance index value reflects to a greater degree of global ventricular dysfunction, but not able to distinguish between systolic or diastolic components (Chao et al., 2009; Ichizuka et al., 2005). Because fetal circulation is ventricle-dominant connecting placenta (Friedman et al., 2003; Boudoulas, 1990) ventricular filling time (VFT) should be considered an important parameter to estimate fetal myocardial index. We have recently reported that timing intervals of PEP, ICT, VET, IRT and VFT for the assessment of fetal cardiac systolic and diastolic performances [which are displayed in Fig. 1] could automatically be estimated by using continuous Doppler Ultrasound signal (DUS) (Marzbanrad et al., 2014, 2016). DUS derived timing intervals were validated with pulsed Doppler based M-mode images (Khandoker et al., 2009; Marzbanrad et al., 2016). In this study, we investigated how DUS derived cardiac systolic, diastolic and myocardial performance indices (TI and modified TI (KI) (Khandoker et al., 2016)) change with normally developed fetuses, and check if DUS derived indices could distinguish sick cases from normal ones from early to late gestational periods.

2. Material and Methods

The study protocol was approved by Tohoku University Institutional Review Board (IRB: 2015-2-80-1) and written informed consent was obtained from all subjects. All experiments were performed in accordance with relevant guidelines and regulations.

2.1. Subjects and signals

Abdominal Electrocardiogram (ECG) and Doppler ultrasound signals (DUS) were collected from 80 pregnant women at Tohoku University Hospital. Out of the total of eighty pregnant women, fifty-five were at the gestational age of sixteen to forty-one (33 ± 6) weeks with normal pregnancy. Twenty-five women had abnormal pregnancy between twenty to thirty-seven gestational age (30 ± 5.6) weeks. Normal datasets were divided into 3 age groups of thirteen early (16–29), 16 mid (30–35) and 26 late (35–41) gestation weeks. The group with abnormal pregnancy symptoms includes various types of CHDs [ventriculoseptal defect (VSD), atrial septal defect (ASD), pulmonary atresia (PA), tetralogy of Fallot (TOF), cardiac dilatation, Ebstain anomaly, bradycardia & tachycardia for sick sinus syndrome (SSS), premature atrial contraction (PAC), AV block, Wolff–Parkinson–White syndrome], and a variety of non-CHDs [Intrauterine growth restriction (IUGR), placental abruption/dysfunction, Hydrops fetalis (non-immune: NIHF and immune: HF)]. All abnormalities were diagnosed by M-mode and B-mode pulse Doppler ultrasound images simultaneously with abdominal fetal ECG signals. Tables 1–2 summarize the demographics for the normal and abnormal cases.

All recordings (each of 1 min length) were sampled at 1 kHz with 16-bit resolution. Tohoku University Institutional Review Board approved the research protocol. Written consents were acquired from all subjects. DUS data were recorded using ultrasonic transducer 5700 (GE Corometrics 116 fetal monitor) with 1.15 MHz signals. Fetal Monitor 116 which can simultaneously record noninvasive fetal ECG and continuous Doppler ultrasound signals (DUS) was developed through a joint collaboration of Atom Medical Co, Tokyo and Tohoku University, Sendai, Japan. Under the research agreement, we were allowed to get access to both raw DUS and fetal ECG signals for research purpose. The position of the Doppler transducer on the abdomen was adjusted for patients to ensure the good quality DUS signals. Output signals were taken through a serial port to a laptop computer. Our previous paper elaborates on the detailed procedure for experimental setup and transabdominal ECG data collection (Sato et al., 2007).

2.2. Automated identification of cardiac valve motions

Fetal ECG (fECG) signals were extracted from abdominal lead ECG signals by using a method for canceling the maternal ECG signal and blind source separation with the reference signal (BSSR) as described in our previous paper (Sato et al., 2007). The DUS signals were decomposed into multi-level wavelet bands, with the use of the second order complex Gaussian as mother wavelet, in order to obtain the aortic and mitral valve motions (Mitral valve closing (Mc); Aorta opening (Ao); Aorta closing (Ac); Mitral valve opening (Mo) times as shown in Fig. 1 upper panel). The detailed signal of the DUS signal at level 2 corresponds to the valve motion events (Fig. 1 lower panel). It is the high frequency component (100–200 Hz) (Marzbanrad et al., 2014). The absolute value of this signal was taken by interpolating its maxima and smoothing by low pass filter. The DUS signals were automatically segmented into cardiac cycle sections with the use of R-peaks of the simultaneously recorded fECG for fetal cardiac timing intervals on beat by beat. A hybrid method was trained from 345 cardiac cycles of DUS components and fECG from 21 fetuses (Khandoker et al., 2016). A combination of Support Vector Machine (SVM) and Hidden Markov Model (HMM) generated the concerned hybrid model. A detailed account can be found in our previous study (Marzbanrad et al., 2014, 2016). The training phase consisted of three sections: the beginning section corresponded to identifying the cluster numbers of DUS components, employing 6 models of the segments of the DUS components that were obtained using K-means clustering; secondly HMM models, which were calculated from the training data of valve motions sequences; and finally, the Support Vector Machine model structure was developed for the identification of valve motions (or the lack thereof). In order to identify the valve events, each signal segment was first matched to the nearest cluster and then trained SVM-HMM specific to corresponding clusters recognized valve motion events. An expert (YK) manually checked and recorded the cardiac valve motion events for this training set based on M-mode pulsed Doppler images.

2.3. Estimation of ICT, IRT, VET and VFT

For all cases, the timings of valve motions (mitral opening and closing, aortic valve opening and closing) were used to determine IRT (mitral opening to aortic valve closing), ICT (mitral closing to aortic valve opening), VET (Ao to Ac) and VFT (mitral opening to mitral closing) beat by beat. The mean values of these intervals over 1 min was estimated for each fetus for further investigation. Tei Index (TI) and modified Tei Index (K-Index or KI) were calculated from (ICT + IRT)/VET and (ICT + IRT)/VFT respectively. The main difference is the denominator of VET in TI

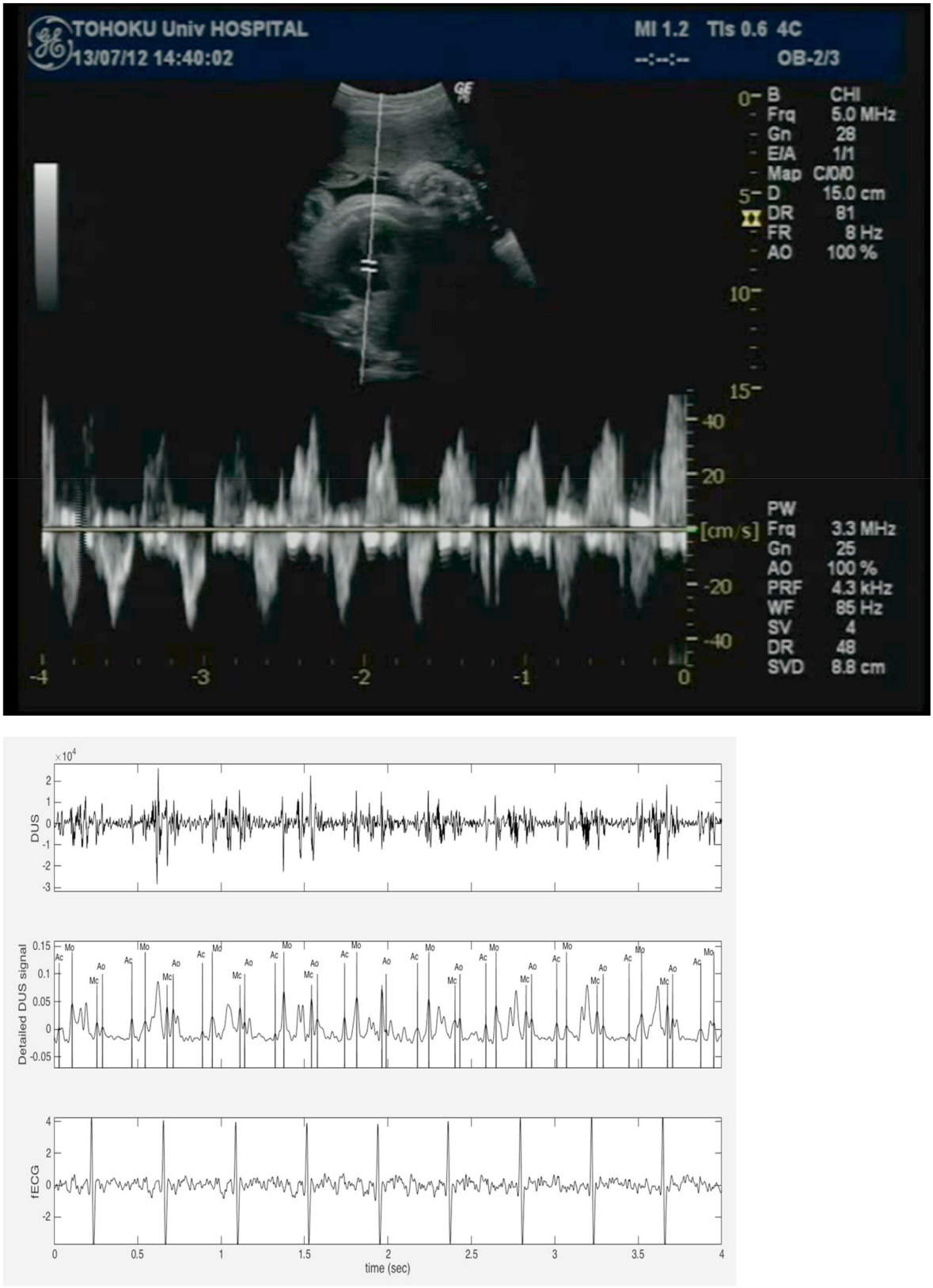

Fig. 1. Upper panel shows Pulse Doppler Image and locations of Fetal cardiac valves' (mitral and aortic) opening and closing timings in relation to fetal ECG cycle and systolic and diastolic intervals. isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), ventricular ejection time (VET) and ventricular filling time (VFT) are shown in the image. The lower panel shows simultaneously identified events: mitral opening and closing (Mo and Mc) and aortic valve opening and closing (Ao and Ac) from raw Doppler Ultrasound Signal (DUS) as shown in the first panel.

Table 1
Demographic data for normal and abnormal fetuses.

Cases	Gestational weeks	Maternal age (years)	Maternal BMI	EFBW	Para	Gravida	Status
Normal Cases							
NE (N = 13)	24.2 ± 4.3	32.6 ± 4.8	21.8 ± 1.6	786.4 ± 563.5	1.7 ± 1.4	0.9 ± 1.2	Normal
NM (N = 16)	32.3 ± 2.0	27.2 ± 5.1	24.2 ± 0.9	1963 ± 572	0.7 ± 0.8	0.2 ± 0.4	Normal
NL (N = 26)	38 ± 1.5	29.8 ± 5.9	23.6 ± 2.7	2727 ± 108.4	0.8 ± 0.9	0.2 ± 0.4	Normal
Abnormal Cases							Abnormality
1	37	40–45	22.7	–	–	–	Bradycardia for SSS
2	31	25–30	23	1623	0	0	IUGR
3	35	35–40	25.3	–	–	–	Acute crisis fetus (Placental abruption)
4	36	30–35	19.7	–	–	–	CHD
5	30	30–35	21	665	3	1	CHD
6	34	30–35	23	2100	1	1	CHD
7	30	35–40	21.5	1157	–	–	Heart failure
8	22	30–35	21.7	–	–	–	CHD
9	22	45–40	21.5	–	–	–	CHD
10	37	25–30	23.6	–	0	0	PAC-IUGR
11	24	40–45	36.2	767	1	1	PA-CAVC-SA-AV block-Polysplenia syndrome
12	24	30–35		449	0	0	Placental dysfunction
13	23	20–25	22.1	–	–	–	VSD-ASD-CDH-Chromosomal aberration
14	33	20–25	26	2600	0	0	Cardiac dilatation-CHD
15	35	25–40	24				AV Block
16	31	30–35	21.8	–	–	–	Medical history of intrauterine fetal death
17	20	30–35	23	428	1	1	NIHF
18	33	35–40	25.5				Fetal Tachycardia
19	35	20–25	25	2373	1	1	WPW
20	29	30–35	22.8	–	–	–	HF
21	35	30–35	21.1	2448	1	1	Fetal Tachycardia
22	28	40–45	22.9	859	1	0	TOF-VSD-PA-MS-PAC
23	26	20–25	24	1332	0	0	Ebstain
24	27	–	–	–	–	–	AV Block- CHD -SA-CAV
25	38	–	–	–	–	–	SSS

NE: normal early group, NM: normal middle group, NL: normal late group, EFBW: Estimated Fetal Birth Weight, C-section: cesarean section. Abnormality abbreviations: 1) SSS: sick sinus syndrome, 2) IUGR: intrauterine growth restriction, 3) CHD: congenital heart defect, 4) TOF: tetralogy of Fallot, *5)* PAC: premature atrial contraction, 6) PA: pulmonary atresia, 7) CAVC: common atrioventricular canal, 8) SA: single atrium, 9) VSD: ventriculoseptal defect, 10) ASD: atrial septal defect, 11) CDH: congenital diaphragmatic hernia, 12) NIHF: non-immune hydrops fetalis, 13) HF: immune hydrops fetalis, 14) WPW: Wolff–Parkinson–White syndrome, 15) MS: mitral stenosis, 16) CAV: cardiac allograft vasculopathy.

and VFT in KI. Because fetal circulation is ventricle-dominant connecting placenta (Friedman et al., 2003; Boudoulas, 1990) ventricular filling time (VFT) was proposed to be included in estimating fetal myocardial index. Lilliefors test was used to check the normality of the data distribution. Statistically significant differences between the normal gestational-age groups were evaluated using 1-way Anova analysis of variance (Kruskal-Wallis test was used when the distribution was not normal), followed by a posthoc test with Tukey-Kramer for multiple comparison. Correlations between gestational ages and myocardial indices of fetuses, were investigated by Spearman correlation coefficient.

3. Results

Tables 1 and 2 show demographics of the normal and abnormal groups. The most common abnormality was CHD (heart anomaly) with its different types (11 cases), followed by atrioventricular (AV) block (3 cases, 2 of them had CHD). A list of the abnormality frequency is given in Table 1. Mean and SD of the cardiac systolic and diastolic intervals for the individual abnormal cases are summarized in Table 2. Fig. 2 shows the scatter plots of the normal and abnormal cases for VFT with IRT, and VFT with VET in three gestational groups (early, mid, late). Generally, the abnormal cases were seen scattered around the normal ones. Some abnormal cases were easily distinguished by their high mean VFT such as the CHD cases with IDs: 9, 11, 13, 23 and 24 and the NIHF (ID: 17) in the early group (two of them had AV clock), the AV block case (ID: 15) in the middle group and the SSS cases (ID: 1, 25) in the late group. Some CHDs were better distinguished by their high mean VET (ID: 9 in the early group and ID: 4 in the late group) or low mean IRT (ID: 4, 5, 9). The two cases with abnormal placenta (ID: 3, 12) were having lower mean IRT compared to normal cases while the two tachycardia cases (ID: 18, 21) were having lower mean VFT. The two IUGR cases were having either low mean VET (ID: 2, mid group) or high mean VFT (ID: 10, late group).

The mean and SD for the cardiac intervals from the three normal gestational groups are summarized in Table 2. The late gestational group had significantly higher mean PEP, ICT and VFT intervals than that of early group. The middle group had significantly higher mean PEP values than that of early group. The only significant difference between the middle and late gestational groups was found in the SD of the VET interval.

The Spearman's correlation coefficients of gestational age with the mean and SD from the cardiac intervals of the normal fetuses are reported in Table 3. The highest correlation (0.50) with age was found in mean PEP (Fig. 3a) followed by mean VFT (0.42, Fig. 3e). Mean ICT and mean fRR were also significantly correlated with age (Fig. 3b,f). The SD was significantly correlated with age only in the IRT interval.

The correlation results between fRR and the other cardiac intervals for the normal groups are summarized in Table 4. For mean ICT, there was a significant correlation with mean fRR only found in the NE group. Mean IRT showed a negative correlation with mean fRR in NE and NL (but not the NM group) as shown in Table 4. For mean VET, the positive correlation was increasing as a function of the gestational age (it was significant in the NM and NL groups. Mean VFT showed high correlation with mean fRR with r value between 0.85 and 0.95 for all three normal groups which resemble a linear relation (Table 4). The SD also showed significant correlation in the NM and NL groups but with lower r value (0.6–0.7).

Relationships between TI and KI indices and the gestational age are shown in Fig. 4. KI had a significant negative correlation with age for the normal group, which was not found with TI.

Table 2
Mean ± SD of the cardiac intervals for the abnormal fetuses and groups of normal fetuses.

Interval		fRR (ms)	PEP (ms)	ICT (ms)	IRT (ms)	VFT (ms)	VET (ms)
Group	values	Normal Cases					
NE	mean	404 ± 20.1	65.3 ± 4.55	33.9 ± 1.61	86.2 ± 8.39	122 ± 23.6	161 ± 6.61
	SD	8.85 ± 4.95	14 ± 3.31[c]	10.6 ± 2.11	20.1 ± 3.85	22.1 ± 4.86	18.9 ± 4.3
NM	mean	417 ± 30.8	71.0 ± 5.27[a]	35.7 ± 3.10	82.9 ± 9.45	136 ± 28.0	162 ± 7.29
	SD	14.9 ± 8.23	15.3 ± 3.85	11.7 ± 2.63	19.9 ± 4.01	26.0 ± 6.75	21.0 ± 4.21
NL	mean	427 ± 27.0	73.4 ± 5.95[a]	36.6 ± 3.37[a]	83.8 ± 7.73	147 ± 27.8[a]	160 ± 6.35
	SD	15.0 ± 12.2[c]	13.6 ± 3.45	11.0 ± 2.44	17.0 ± 4.15	23.9 ± 9.94[c]	17.8 ± 4.69[b,c]
ID	Number of Cardiac cycles	Abnormal cases					
1	103	572 ± 50.4	66.2 ± 19.5	35.5 ± 14.7	82.8 ± 104[b]	282 ± 57.3	160 ± 22.2[b]
2	155	386 ± 14.1	71.9 ± 13.1[b]	35.1 ± 10.6	68.8 ± 98.3[b]	117 ± 26.1[b]	149 ± 17.4[b]
3	156	395 ± 6.64	73.4 ± 14.9	39.4 ± 14.4	51.3 ± 63.8	147 ± 13.7	149 ± 15.9
4	96	414 ± 17.1	70.5 ± 19.6	34.9 ± 14.2	62 ± 80.8	135 ± 25[b]	170 ± 21.2[b]
5	134	445 ± 19.1	63.4 ± 14	35.3 ± 11.3	58 ± 79.5	174 ± 19.7	166 ± 20.1
6	150	395 ± 3.89	79.1 ± 18.3	36.3 ± 13.2	79 ± 104	103 ± 19.4	162 ± 20.1
7	120	404 ± 17.2	73.1 ± 13.8[b]	32.8 ± 10.5	53 ± 74.5[b]	142 ± 18.4[b]	164 ± 17.4[b]
8	132	450 ± 65.7[b]	71.8 ± 18.9[b]	36.3 ± 13.7	69.3 ± 101[b]	167 ± 65.2[b]	161 ± 25.2
9	122	491 ± 150	65.1 ± 13.1	33 ± 11.4	60 ± 93	217 ± 147	172 ± 25.4
10	116	514 ± 670	64 ± 13.7[b]	34 ± 9.83	76.5 ± 99	228 ± 673	162 ± 17.2
11	61	963 ± 167	61.2 ± 15	33.7 ± 9.7	75 ± 104[b]	669 ± 160	168 ± 22.4[b]
12	146	409 ± 5.23	65.3 ± 9.87	28.8 ± 6.46	56 ± 68	140 ± 19.4	174 ± 11
13	67	890 ± 8.74[b]	73.6 ± 13.2[b]	35.5 ± 11.3	76 ± 104[b]	608 ± 25.8[b]	162 ± 56.1
14	122	490 ± 171	72.7 ± 20.5	35.7 ± 14.9	76 ± 101	202 ± 176	166 ± 28.3
15	64	919 ± 337	67.3 ± 17.1[b]	34.1 ± 13.2	82 ± 102	634 ± 341	154 ± 21.8[b]
16	162	367 ± 12.7	62.5 ± 11.9	32.1 ± 8.5	83 ± 110[b]	88.3 ± 21.8[b]	150 ± 18.8[b]
17	77	770 ± 292	68.3 ± 14.7[b]	34.2 ± 12.5	73.5 ± 106[b]	499 ± 285	160 ± 22.5[b]
18	200	297 ± 71	82.1 ± 15.3[b]	35.3 ± 11.8	53 ± 74	71 ± 71.7	140 ± 23.9[b]
19	137	435 ± 15.4	83 ± 15[b]	34 ± 10.8	64.8 ± 84.3	158 ± 26.7[b]	168 ± 18.2[b]
20	143	417 ± 10.3	72 ± 18.7	35.5 ± 12.7	74 ± 108[b]	133 ± 29.9[b]	159 ± 26.7
21	175	342 ± 17.1	75.3 ± 14.7	36.6 ± 11.8	65.5 ± 96.5	76.8 ± 23.3[b]	148 ± 21.9
22	144	414 ± 96	66.2 ± 17.6[b]	35.3 ± 15	76 ± 101	122 ± 98.3	168 ± 20.4[b]
23	84	472 ± 16.1	66.8 ± 16.6[b]	37.8 ± 14.3	78 ± 96[b]	188 ± 21.9	162 ± 20.3[b]
24	67	885 ± 216	72.6 ± 13.2[b]	32.4 ± 10.9	70.3 ± 106[b]	607 ± 214	160 ± 24.1[b]
25	103	577 ± 285	64.5 ± 19.5	35.7 ± 13.2	85.3 ± 102	292 ± 287	162 ± 22.3[b]

†: PEP: pre-ejection period, ICT: isovolumetric contraction time, IRT: isovolumetric relaxation time, VET: ventricular ejection time, VFT: ventricular filling time, fRR: Fetal RR, HR: heart rate in beat per minute (bpm), SD: standard deviation, NE: normal early gestational group, NM: normal middle gestational group, NL: normal late gestational group.

[a] Significantly different from NE ($p < 0.05$).

[b] Significantly different from NM ($p < 0.05$).

[c] Not normally distributed data.

4. Discussion

Accurate prenatal diagnosis of CHD is critical to many cases when aggressive management and therapy are required after birth. This study assessed phenomena of diastolic and systolic functions in developing fetal heart. To this end, fetal myocardial performance indices were made use of. These indices were estimated from Fetal ECG and DUS signals. The proposed method generates more accurate measurements of electromechanical valve timing intervals. In comparison with the pulsed Doppler and traditional M-mode, this method is not only cost effective and employ simple techniques. This study investigated congenital structural defects and heart beat anomalies associated with conduction problem. Structural defects included problematic valves that are responsible for filling and squeezing blood, or a defective heart septum. Most common heart defects, such as pathologies between the chambers (atrial septal defect, ventricular septal defect) and even more complex conditions such as transposition of the great arteries and tetralogy of Fallot that cause too little blood to travel to the body and the lungs (Congenital Heart Disease, 2020). These defects are a result of underdeveloped chambers of the heart or blockages in blood vessels that prevent the proper amount of blood from traveling to the body to meet its needs. The body does not get enough oxygen with these heart problems. CHD may also involve the conduction system of the heart, which is responsible for making the heart beat at a normal rate [120–160 bpm] including Fetal tachycardia, PAC, AV block, SSS and WPW. Fetal arrhythmias are generally defined as an irregularity of the cardiac rhythm (Ibrahim et al., 2017). In addition to common CHDs, non-CHD cases including IUGR, Hydrops Fetalis and Placenta abruption were also investigated in this study. Some of the findings are discussed in the following paragraphs.

4.1. Fetal myocardial performance indices in normal fetuses

Positive significant correlations of PEP, ICT, VFT and fRR with gestational ages (as shown in Fig. 3) are evident in normal growing fetuses. The highest correlation with age was found to be with PEP ($r = 0.5$, $p < 0.01$). In particular, while increasing PEP reflects in ejection time remaining the same or decreasing during each cardiac cycle which could mean the increasing stroke volume during gestation. The recent study by Mensah–Brown et al. has shown that PEP increases with the gestational age ($r = 0.57$, $p < 0.0001$) (Mensah-Brown et al., 2010). While most systolic time intervals increase with gestational age, it is notable that VET did not increase and in fact showed a decrease that was not statistically significant. Inverse correlation of KI values with fetal age (Fig. 4b) could mean that an increasing heart size requires a longer time to fill in the left ventricle. Because VET and IRT did not show any significant correlations with fetal age, TI eventually did not show any significant correlation with age as shown in Fig. 4a. It could be speculated that biomechanical constraints in ventricular blood flow due to continuous inward oxygenated blood flow from placenta could drive the high correlation values with fRR indicating the association with autonomic nervous system. Correlations of VET with fRR intervals were significant at mid and late gestational ages, which were also found previous research on adult VET values (Mäkikallio et al., 2005).

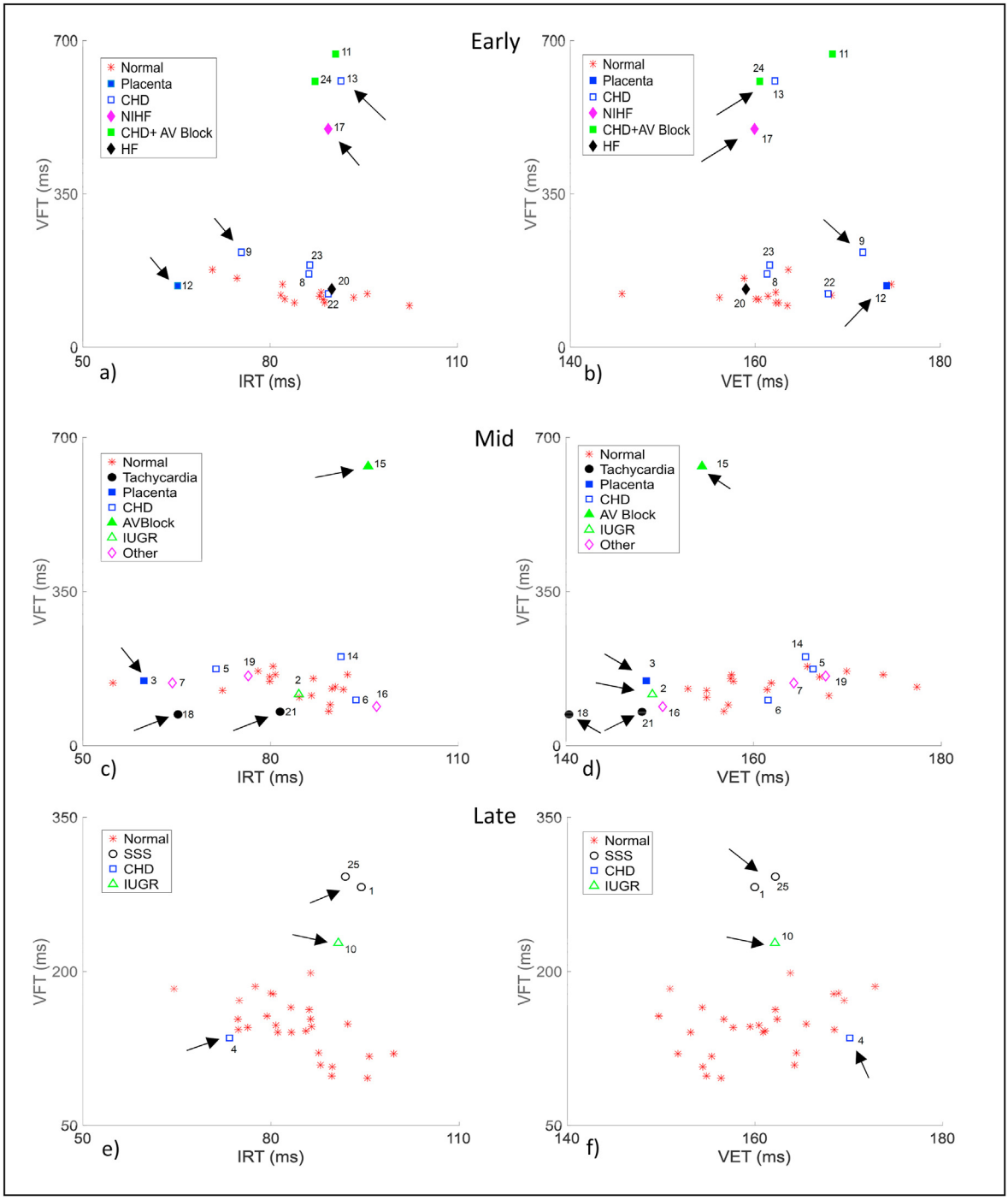

Fig. 2. Plots of mean VFT vs. mean IRT for early (a) middle (c) and late (e) gestational weeks and mean VFT vs. mean VET for early (b) middle (d) and late (f) gestational weeks. The numbers indicate IDs of abnormal cases. The arrows indicate abnormal cases of interest.

Table 3
Spearman's correlation between age and the myocardial intervals features for the normal fetuses.

Interval	mean	SD
PEP	0.50†	−0.1
ICT	0.35†	0.03
IRT	−0.22	−0.34[a]
VET	−0.16	−0.19
VFT	0.42†	−0.03
fRR	0.37†	0.18

Correlations of IRT with fRR intervals were negative, however, in the mid gestation cases the correlation value was very low ($r = -0.08$) as compared to early and late groups ($r = -0.52$ and -0.52 respectively). Heart rate determines how much time available for ventricular filling. As heart rate decreases during gestation, the time spent in diastole increases relative to systole causing VFT to increase. VFT follows RR intervals to match the cardiac output with venous return according to Frank-Starling mechanism (Widmaier et al., 2016). Reduced compliance of the ventricle wall makes an inadequate filling of the ventricle which causes a decrease in the end-diastolic volume. The reduced end-diastolic volume then causes a reduction in stroke volume because of the Frank-Starling mechanism (Widmaier et al., 2016). It is important to note that in

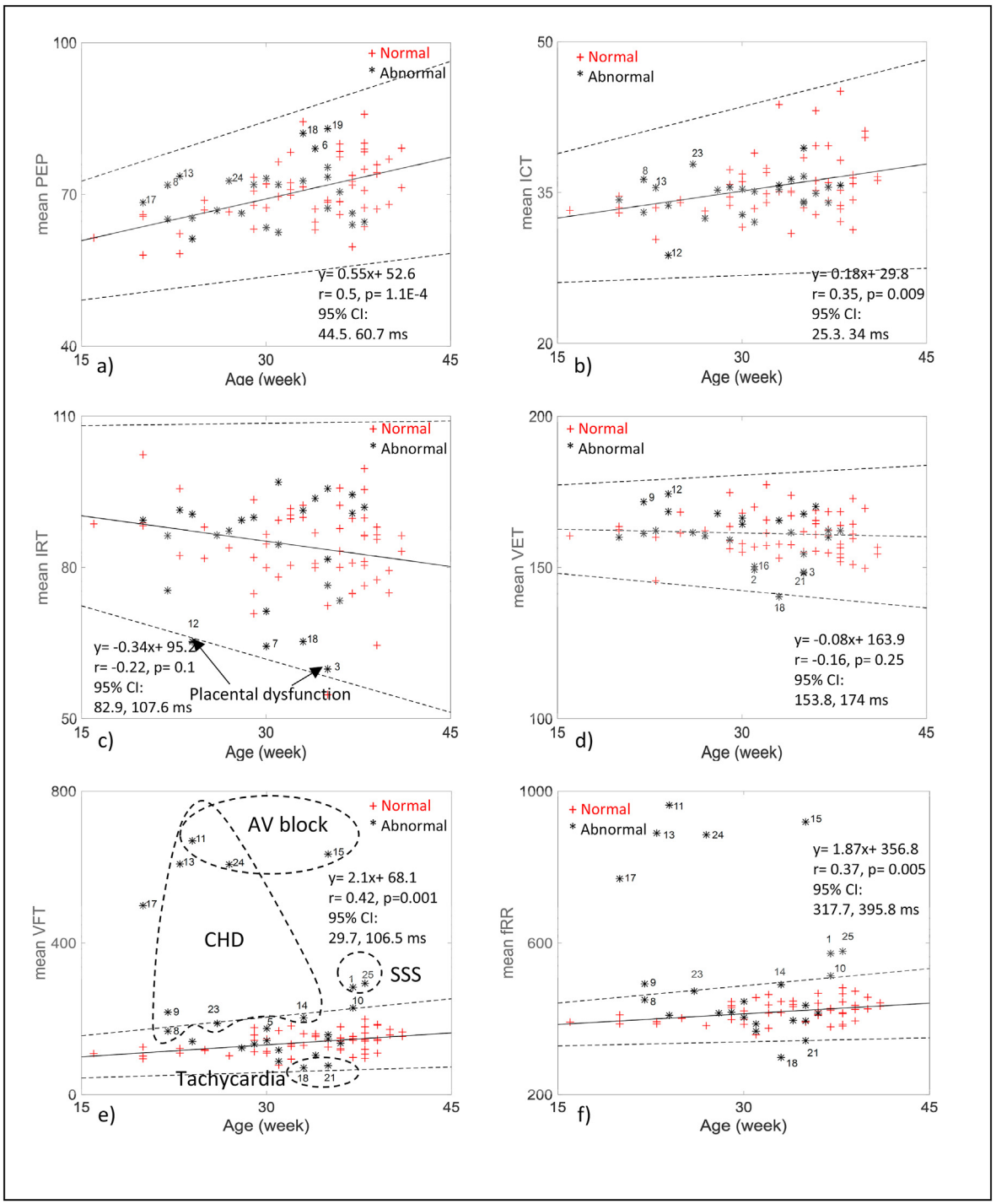

Fig. 3. Mean of the six cardiac intervals vs. gestational weeks for normal and abnormal fetuses. Dashed lines indicate the 95% confidence limits. PEP, ICT, VFT and fRR showed significant positive correlation with age. The numbers indicate IDs of abnormal cases. The equations represent the linear fit for the normal fetuses.

clinical studies on adults it was found that VFT is controlled by both sympathetic and parasympathetic activity (Khandoker et al., 2016; Pinsky, 2005; Frazier et al., 2008).

4.2. CHD: Structural defects

Generally CHD cases (Table 1: ID 8,9,11,13,14,23,24) have higher mean RR and VFT than the normal ones as shown in Fig. 3e and f). CHDs with AV block (ID 11, 13, 24) have higher VFT values (Fig. 2 a,b; Fig. 3e and f), which make them distinct from the early normal fetal group. Other CHD cases (ID 8,9,14,23) showed slight increases in VFT and RR values. Among them ID 23 had Ebstein's anomaly which is a CHD in which the septal and posterior leaflets of the tricuspid valve are displaced towards the apex of the right ventricle of the heart (Jost et al., 2007). ID 22 of Tetralogy of Fallot is shown to have higher mean and SD of VFT and RR. Dysfunction of the control system in heart anomaly could be considered factors behind the differences in correlation parameters. The precise explanation requires further prospective research study, which will be attempted in the future study.

Table 4
Spearman's correlation between fRR and the other myocardial intervals for the normal gestational groups.

Interval	mean	SD
PEP		
NE	0.46	−0.35
NM	−0.31	0.24
NL	−0.18	0.15
ICT		
NE	0.86†	0.42
NM	0.11	0.21
NL	0.15	0.09
IRT		
NE	−0.52	0.41
NM	−0.08	0.17
NL	−0.52†	0.31
VET		
NE	0.37	0.14
NM	0.63†	0.40
NL	0.49[a]	0.21
VFT		
NE	0.84†	0.19
NM	0.95†	0.66†
NL	0.95†	0.72†

[a] , † indicate significant correlation with $p < 0.05$ and $p < 0.01$ respectively.

4.3. CHD: defects in conduction pathways

4.3.1. Fetal tachycardia

Fetal tachycardia is defined as a heart rate above 160–180 beats per minute (bpm) and typically ranges between 170 and 220 bpm (Oudijk et al., 2020). The estimated prevalence is 0.4–1% of pregnancies (Bergmans et al., 1985). In the majority of cases, the abnormal electrical impulses originate from the atria (Oudijk et al., 2020). ID 18, 21 are shown to have lower VFT, VET, IRT (Fig. 2c and d; Fig. 3e,d,c), IRT (ID 18) along with lower RR (Fig. 3f). Heart rate determines how much time available for ventricular filling and cardiac output. An increase in heart rate (decrease in RR interval) shortens the diastolic filling time. Under tachycardic conditions, impaired diastolic functioning can be improved by reducing heart rate, which provides a longer time for filling. When heart rate exceeds 180 bpm, diastolic filling time is so short that cardiac output usually falls reflecting lower VFT because of overuse of cellular substrate to cause a decrease in the strength of contraction (Moser and Riegel, 2007).

4.3.2. Atrioventricular (AV) block and sick sinus syndrome (SSS)

A fetal ECG can detect first-degree AV block in the fetus. ID 11, 14, 24 (AV block cases) as well as SSS (ID 1 and 25) which were shown to have higher mean and SD VFT and RR (Fig. 3 e,f). SSS is defined as an arrhythmia type attributed to sinus node abnormalities and is clinically diagnosed by electrocardiographic demonstration of inappropriate sinus bradycardia, sinus arrest, or chronotropic incompetence (Benson et al., 2003; Moss et al., 2001).

4.3.3. Intrauterine growth restriction (IUGR)

IUGR affects 3–10% of pregnancies and 20% of stillborn infants have IUGR (IUGR statistics, 2018). Ultrasound is the benchmark for accurate pregnancy dating and diagnosis of IUGR (Bamfo and Odibo, 2011). ID 2 (IUGR) has lower VET (Fig. 2d) and ID 10 (IUGR + PAC) has higher mean VFT (Fig. 2f) reflecting in higher mean RR intervals. In the fetus with IUGR, It was also reported that in the mammalian myocardium the main determinant of ventricular ejection is afterload (placental vascular resistance) and the determinant of ventricular filling is preload (venous return) (Al-Ghazali et al., 1988; Tsyvian et al., 1998). Therefore, we speculate that lower preload and elevated afterload could be considered the main cause of VET decrease and VFT increase an in the growth restricted fetus. ID 10 has comorbid PAC that is a premature contraction generated from the atria causing faster electrical impulse coming earlier than normal conduction, and in most cases, causes an extra contraction of the heart. The conductions arise in atrium and can be either transmitted to the ventricles or blocked. The prevalence of PAC is 1–2% of cases with a congenital cardiac anomaly (Pilu et al., 1999).

4.3.4. Hydrops fetalis

A non-immune case (ID 17) is shown to have higher VFT and RR than that of an immune case (ID 20) which could be due to weak ventricular force (Fig. 2b). Diastolic failure in hydrops fetalis appears when the ventricle can't be filled properly because it can't relax or because its wall is thick or rigid. Higher myocardial performance indices correlate with worse outcomes for fetuses with hydrops fetalis (Falkensammer et al., 2001). KI Index of ID 17 was shown to be very low (Fig. 4b) as compared to normal cases. On the other hand, TI could not distinguish it from the normal cases. Additionally changes in ventricular filling which usually impede venous return from the placenta, were also reported to be in placental edema resulting in the evolution of fetal hydrops (Barrea et al., 2005).

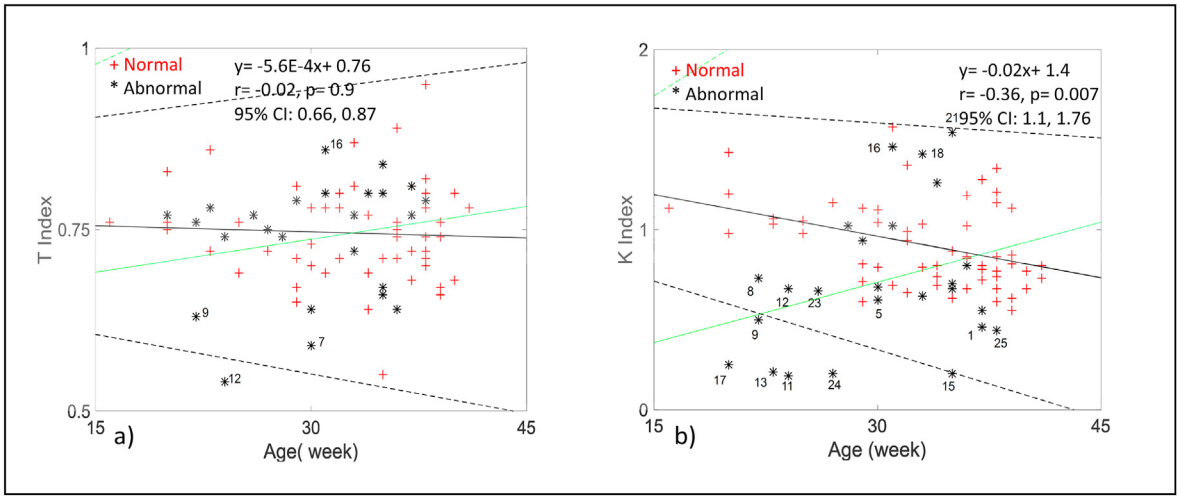

Fig. 4. TI (a) and KI (b) vs. gestational weeks for normal and abnormal fetuses. Dashed lines indicate the 95% confidence limits. KI had a significant negative correlation with age for the normal group which was not found in TI.

4.3.5. Placental abruption

IRT measures ventricular relaxation, which also correlates with invasive indices (Myreng and Smiseth, 1990). ID 3, 12 were the cases of Placental abruption which is a serious complication of late pregnancy bleeding, wherein the placental lining has separated from the uterus of the mother prior to delivery (Cunningham). IRT values of the two cases were found to be lower than the same in normal cases (Fig. 2a,c and Fig. 3c). It remains to determine whether placental abruption or placental damage causes cardiovascular remodeling associated diastolic function.

5. Conclusion

In this study normal values of Tei Index (TI) and modified TI (KI) for systolic and diastolic performance in early (<30 weeks), Mid (30–35 weeks) and late (36–41 weeks) relating to both normal fetuses (55 cases) as well as fetuses carrying a variety of fetal abnormalities (25 cases) were successfully estimated by using simultaneously recorded Fetal Electrocardiogram Signals (FES) and Doppler Ultrasound Signal (DUS). Modified TI (KI) may be a useful index to monitor the normal development of fetal myocardial function and identify fetuses with a variety of CHD and non-CHD cases. Given the discussion above and given the affordability of traditional ultrasound scans and fetal echocardiograms for mass screening of all pregnancies due to various economic reasons and the shortage of trained sonographers, the present study results could open up the possibilities of the development of simple Doppler derived myocardial indices for clinical use which may eventually serve as a pre-clinical or even clinical step in prenatal low-risk screening and in overall diagnostic algorithms for sick fetuses.

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Consent for publication

Not applicable.

Data availability

Data used in this study will be made available upon request because we did not have any approval from ethics committee to make the data publicly available. The pregnant mothers recruited for this study did not give consent to make their data and signals available in the public domain. However, the following persons can be contacted to obtain the data under a confidentiality agreement. Dr Ahsan Khandoker (ahsan.khandoker@kustar.ac.ae); Dr Yoshitaka Kimura (ykimura@med.tohoku.ac.jp).

CRediT authorship contribution statement

Ahsan H. Khandoker: Conceptualization, Methodology, Validation, Writing - original draft, Writing - review & editing, Funding acquisition. **Haitham M. Al-Angari:** Formal analysis, Validation, Writing - original draft, Visualization, Writing - review & editing. **Faezeh Marzbanrad:** Conceptualization, Methodology, Software, Writing - review & editing. **Yoshitaka Kimura:** Conceptualization, Methodology, Investigation, Validation, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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