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Normal reference ranges for fetal cardiac function: Assessed by modified Doppler myocardial performance index (Mod MPI) in the Egyptian population

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ABSTRACT

Aim: To develop gestational age-based reference ranges for the modified Doppler myocardial performance index (Mod MPI) and to examine the maternal characteristics that affect this measurement.
Methods: This was a cross-sectional study, comprised of 1021 healthy pregnancies between 20+0 to 35+6 weeks' gestation. They were all undergoing ultrasound examination in Cairo Fetal Medicine Unit (CAIFM) in Cairo University, Egypt from 1st April 2017 till 1st April 2019. Mod MPI was obtained used method described by Friedman et al. (2003).
Median and SD models were fitted between Mod MPI and gestational age. The distributions of Mod MPI Z-scores were examined in relation to maternal characteristics
Results: The normal Mod MPI in second and third trimester (20 + 1 to 35 + 6 weeks' gestation) was 0.408 ± 0.08. Mod MPI was not affected by maternal age, body mass index (BMI) or parity (*p* value 0.5, 0.6 and 0.2 respectively).
Conclusion: This study established normal reference ranges for Mod MPI according to gestational age and generated a graph with 5th,10th, 90th and 95th centiles. Maternal characteristics as age, BMI or parity do not affect value of Mod MPI.

Introduction

Functional fetal cardiac evaluation has been a goal of many fetal medicine researchers for a long time. Improvements in ultrasound imaging led to morphological cardiac examination being part of routine fetal surveillance [1].

However, there are some challenges regarding methods of fetal cardiac function measurement. Most of cardiac function measurements have been considered difficult, poorly reproducible, and technically challenging [2].

In 1995, Tei et al. described an easily measured Doppler-derived index that incorporates both systolic and diastolic time intervals in expressing global systolic and diastolic ventricular function [3].

The myocardial performance index (MPI) is defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by ejection time (ET). The MPI provides information on the different time periods during the systolic phase of the cardiac cycle, therefore, it is less dependent of both heart rate or ventricular anatomy [3,4].

The MPI has been reported to be a simple, reproducible non-invasive, Doppler-derived myocardial performance index. The MPI can be used to assess left as well as right ventricular function [4].

The MPI was initially used in adult population in clinical evaluation in cardiac amyloidosis. Soon after, MPI was reported in the literature in the assessment of myocardial performance in adults as well as paediatric population and then in assessment of fetal cardiac function. MPI was used in variety of clinical conditions including myocardial infarction([5]), dilated cardiomyopathy [3] and amyloidosis [4] and in those with congenital heart disease (CHD) with single ventricle physiology([6]); as well as in paediatric patients who have undergone a cardiac transplant [7].

In the fetal population, MPI was first used by Tsutsumi et al. in 1999 to evaluate fetal cardiac performance [[8]. There was wide range of reported TI values in different studies. Researchers

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believed that the MPI and its modifications are a potentially useful method of estimating fetal cardiac adaptive changes in complicated pregnancies [8–10]. The MPI and its modification have been used in a number of pathological conditions, including intrauterine growth restriction [8,11–14], maternal diabetes [15–19], twin-twin transfusion syndrome (TTTS) [20–23], congenital heart malformations [24–28], pre-eclampsia [29], and other fetal conditions [30–33].

Researchers noticed that the results showed a wide variation in the normal reference values, ranging from 0.35 to 0.60 as mean value [10]. This variation can be explained mostly due to the lack of clear landmarks in the Doppler waveforms to calculate the time-periods. Friedman et al. suggested that the MPI could be evaluated from a single Doppler waveform, with the advantage of individually estimating the isovolumetric contraction time (ICT) and the isovolumetric relaxation time (IRT) [34]. Raboisson et al. developed a modification of the approach created by Friedman using the Doppler echo of the opening of the aortic valve (AV) as a landmark to better estimate the limits between the time periods of the MPI calculation, this technique is the modified MPI (Mod MPI) [35].

The objectives of this study were, first, to develop gestational age-based reference ranges for Mod MPI and, second, to examine maternal characteristics that might affect the Mod MPI.

Methods

Patient selection

This cross-sectional study was performed in Cairo Fetal Medicine Unit (CAIFM) in Cairo University and was approved by the Medical Ethical Committee of the Obstetrics & Gynaecology Department at Cairo University. The study was registered with clinical trials under number NCT03169907.

The study group consisted of 1021 healthy pregnancies between 20 + 0 and 35 + 6 weeks' gestation undergoing ultrasound examinations in the Fetal Medicine Unit (CAIFM) between April 2017 till April 2019. Recording of maternal demographic characteristics, medical and obstetric history was recorded at each scan in medical records. Maternal height and weight were measured and recorded also.

The ultrasound examinations were carried out by 3 sonographers (AO, SE, NS) who had extensive training in ultrasound scanning and had obtained the Fetal Medicine Foundation Certificate of Competence in Doppler ultrasound. All measurements were double checked and rectified by AE who has Diploma in fetal medicine awarded by Fetal medicine foundation (FMF).

The inclusion criteria were singleton pregnancy with no fetal anomaly, not IUGR, not small for gestational age and the mother free of medical disorder. The pregnancy was dated by fetal crown–rump length at 11 + 0 to 13 + 6 weeks' gestation. We excluded women with known medical conditions or pregnancy complications as pre-eclampsia or small for gestational age. All pregnant women had a detailed anomaly scan including fetal echocardiography. All scans were performed trans-abdominally using GE Voluson E10 (General Electric, Chicago, IL, USA).

The Mod MPI was obtained in all subjects. We used the technique described by HERNANDEZ-ANDRADE *et al.* to obtain Mod MPI as shown in Fig. 1 (36). All measurements were done in the absence of fetal movements nor respiratory movements where the mother involuntarily suspended respiration. The velocity of the Doppler sweep on the ultrasound screen was the highest velocity available (15 cm/s) for clear identification of the components of the Doppler tracing. Additionally, the E/A waveform was always displayed as positive flow. The angle of insonation was always kept below 30◦ and the mechanical and thermal indices were not exceeded 1. A cross-sectional image of the fetal thorax in the four-chamber view and an apical projection (anterior or posterior) of the heart were obtained (Fig. 1). We were using the Modified Myocardial Performance Index where the Doppler sample volume was placed on the lateral wall of the ascending aorta, below the AV and just above the MV. The Doppler trace which showed a clear echo corresponding to the opening and closure of the two valves at the beginning and at the end of the E/A (mitral valve) and AF (aortic valve) waveforms (Fig. 2 and 3). The time periods were then estimated as follows: the ICT was estimated from the closure of the MV, to the opening of the AV, the ET from the opening to the closure of the AV, and the IRT from the closure of the AV to the opening of the MV (Fig. 3). The final result for the Mod-MPI was calculated as: (ICT + IRT)/ET (34,35,40) (Fig. 4).

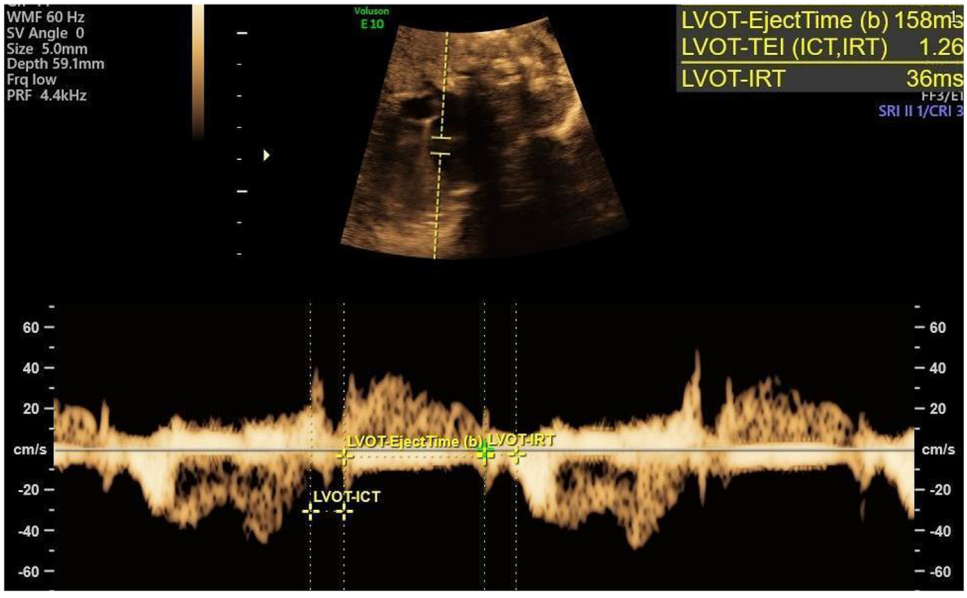

Fig. 1. The corresponding Doppler waveform is shown at the bottom and the 2D echocardiograph is at the top.

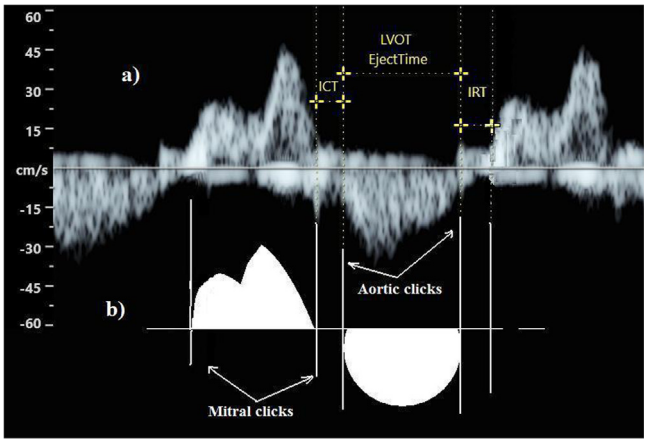

Fig. 2. Schematic representation of Mod MPI measurement. The arrows indicate the presence of valve clicks (a). The ICT is delimited from the closure of the mitral valve to the aortic valve opening, the IRT from the closure of the aortic valve to the mitral valve opening, and the ET from the opening to the closure of the aortic valve. The callipers must be placed just before the echo of each valve click, avoiding overlapping with the valve echo white area (b). Adopted from Cruz-Martínez et al. [37] with slight modification.

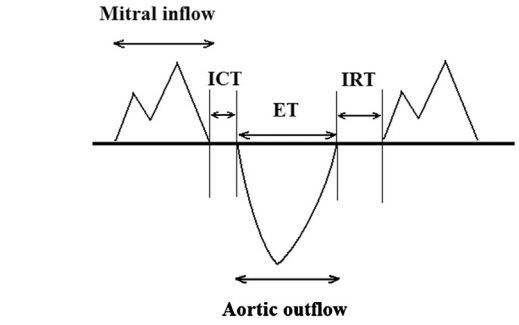

Fig. 3. Time interval measurements are based upon the echoes from valve movements. Adopted from Priya Maheshwari et al. [40] with slight modification.

Table 1
Characteristics of study population of 1021 pregnancies.

Variable	Obs	Mean	Std	Min	Max
Age	1021	29.9	5.87	18	42
Gravidity	1021	2.5	1.49	1	11
Parity	1021	1.13	1.17	0	8
BMI	1021	26.8	2.7	19	35

Statistical analysis

Median and SD models were fitted for the Mod MPI with gestational age, assuming a $\log_{10}$ Gaussian distribution. The median was obtained by regression analysis; plots of GA *vs* daily medians of the Mod MPI was used to identify suitable polynomial forms. For estimation of SDs, log transformations were first used to make the variation about the median more stable and symmetric. Quadratic regression models were then fitted to the SDs; the SDs for each gestational day were estimated using the median absolute deviation from the median. Assessment of goodness of fit of the models was by inspection of quantile-to-quantile (*Q*–*Q*) plots of *Z*-scores calculated using the mean and SD models.

The distributions of the Mod MPI *Z*-scores were examined in relation to maternal age, body mass index (BMI) and parity (parous or nulliparous if no previous pregnancy at ≥28weeks).

The statistical software package used was SPSS 13.0 (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered statistically significant.

Results

Pregnancy characteristics of the studied 1021 singleton pregnancies are summarized in Table 1.

The fetal ICT, IRT and ET were easily obtained in all 1021 cases. The Mod MPI was calculated from the above measured data (TI = ICT + IRT/ET). The mean Mod MPI was 0.408 ± 0.08 for 20–35 weeks of gestation (Table 2).

The Mod MPI appeared to be independent of GA (Fig. 5). There was no correlation between Mod MPI and maternal age, BMI or parity (*p* value 0.5, 0.6 and 0.2 respectively).

The *Q*–*Q* plots demonstrate that the goodness of fit of the models was generally acceptable. The 5th, 10th, 25th, 50th, 75th,

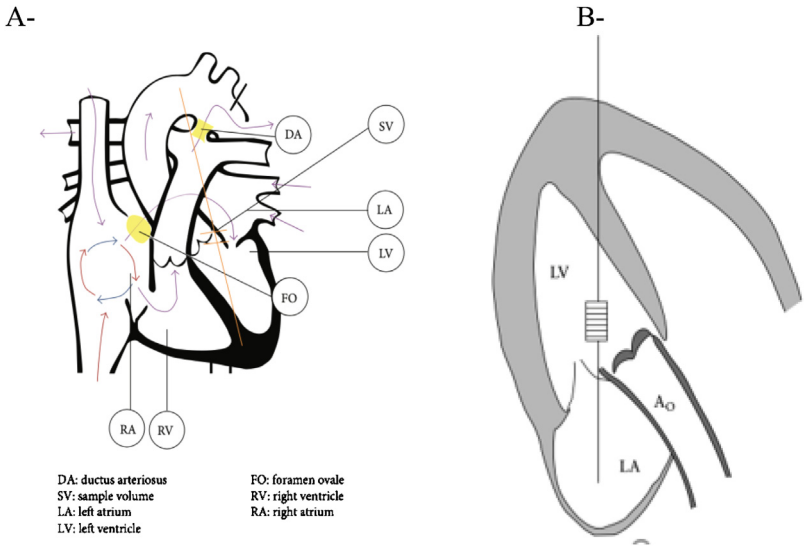

Fig. 4. The schematic diagram shows placement of the Doppler sample volume (SV) in left Mod-MPI measurement. (A) Adopted from Priya Maheshwari et al. [40]. (B) Adopted Friedman et al. [34].

Table 2
statistical summary The 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles of Mod MPI according to gestational age from mid-gestation for each week between 20 and 35 weeks.

	20 wks	21 wks	22 wks	23 wks	24 wks	25 wks	26 wks	27 wks	28 wks	29 wks	30 wks	31 wks	32 wks	33 wks	34 wks	35 wks
Cases	51	50	54	68	116	86	68	53	53	58	56	59	65	70	62	52
Mean	0.3853	0.431	0.4069	0.3919	0.4028	0.4105	0.4044	0.4038	0.4036	0.4248	0.4091	0.4071	0.4026	0.4014	0.4447	0.4125
Median	0.37	0.415	0.39	0.38	0.395	0.4	0.39	0.38	0.39	0.42	0.385	0.38	0.38	0.38	0.43	0.38
Variance	0.006	0.011	0.009	0.006	0.006	0.007	0.006	0.009	0.006	0.007	0.007	0.006	0.006	0.005	0.007	0.007
Minimum	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.3	0.29	0.29	0.3	0.29	0.3	0.31	0.29
Maximum	0.62	0.66	0.63	0.61	0.67	0.65	0.64	0.6	0.62	0.62	0.62	0.6	0.61	0.6	0.61	0.63
Percentiles																
5	0.3	0.3	0.29	0.3	0.3	0.2935	0.2945	0.297	0.3	0.2995	0.3	0.3	0.3	0.31	0.35	0.31
10	0.31	0.301	0.3	0.3	0.32	0.3	0.32	0.3	0.3	0.3	0.327	0.33	0.33	0.33	0.35	0.31
25	0.33	0.34	0.33	0.33	0.34	0.35	0.3525	0.325	0.35	0.345	0.3525	0.35	0.36	0.34	0.3775	0.3425
50	0.37	0.415	0.39	0.38	0.395	0.4	0.39	0.38	0.39	0.42	0.385	0.38	0.38	0.38	0.43	0.38
75	0.42	0.5125	0.4625	0.4275	0.43	0.4325	0.42	0.46	0.43	0.51	0.45	0.44	0.435	0.44	0.5125	0.48
90	0.5	0.6	0.56	0.51	0.543	0.53	0.531	0.566	0.54	0.541	0.553	0.55	0.528	0.51	0.57	0.534
95	0.574	0.6345	0.6125	0.5365	0.58	0.593	0.5655	0.593	0.556	0.5605	0.583	0.58	0.577	0.57	0.6	0.6

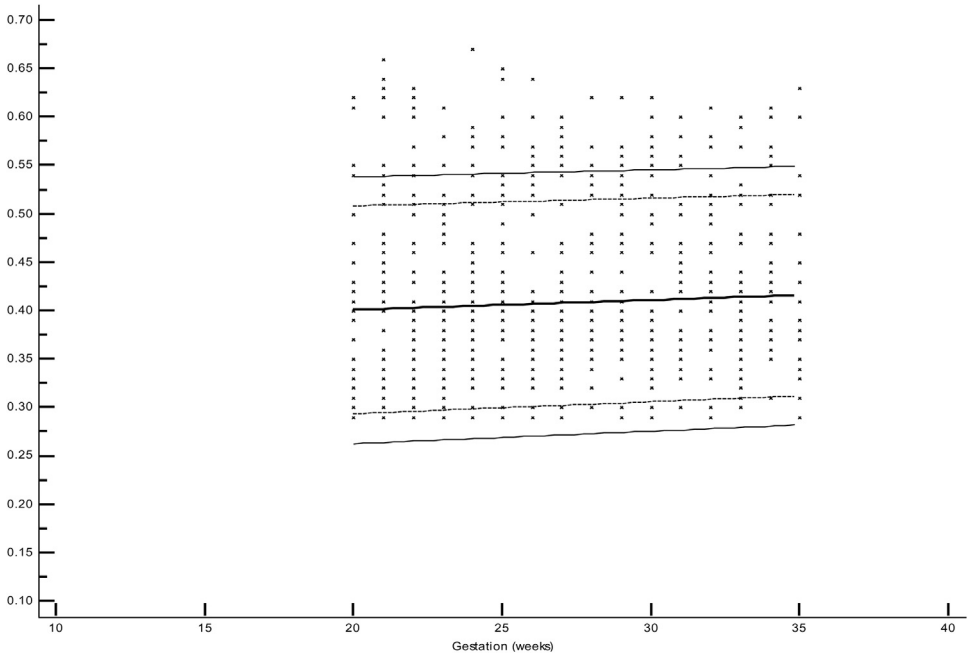

Fig. 5. Plots of the MPI against GA. 5th, 10th, 50th, 90th and 95th centiles shown.

90th and 95th percentiles of Mod MPI according to gestational age from mid-gestation for each week between 20 and 35 weeks are shown in Table 2. The 5th, 10th, 50th, 90th and 95th centiles are shown in Fig. 5 and 6. The median Mod MPI seemed relatively stable and vary slightly from 20 weeks to 35 weeks gestational age (Fig. 6).

Discussion

Principal findings of study

This study has established normal reference ranges according to gestational age for Mod MPI. In our low risk population, median Mod MPI was independent of maternal age, BMI and parity.

In the construction of the reference ranges, we choose a log Gaussian model for simplicity and to facilitate the calculation of *Z*-scores. We found that, after allowing for gestational age, there were no significant effects on Mod MPI from maternal age, BMI and parity.

Comparison with previous studies

Normal reference values and the reproducibility of the left Tei index have been published before [37–39].

Tsutsumi et al. were the first to report using the TI to assess fetal global myocardial function. Our data are slightly different to those of Tsutsumi et al. Their LV TI was 0.62 ± 0.07 (18–26 weeks). After 34 weeks' gestation, they found that the LV TI fell to 0.43 ± 0.037. Our results are slightly different in 20–26 weeks range; However, our results are very similar to their results after 34 weeks. They suggested that the maturational changes in the LV properties in human fetuses accelerate after late gestation and that the global changes in ventricular function may relate to developmental changes of the fetal myocardium in late gestation(8). They did their study on 50 normal pregnancies.

Our data does not support that the global LV function change with gestational age. Other data in the literature agree with our study as Friedman et al, Mori et al. and Eidem et al. (30, 34).

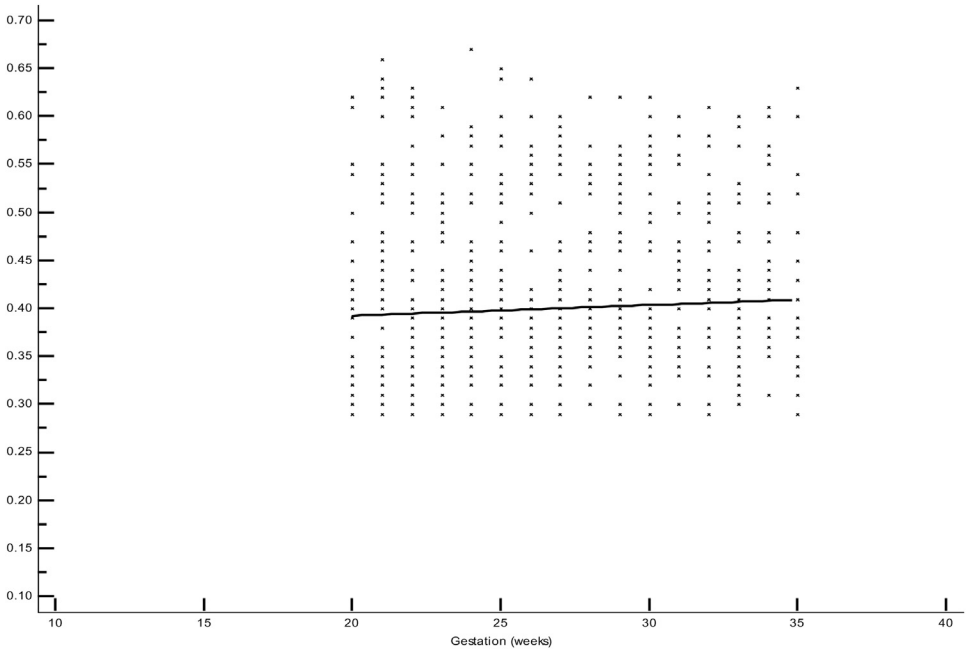

Fig. 6. Plots of the MPI against GA.

However, their report mean of TI was slightly lower than our mean. Friedman et al. in 2003 reported the normal TI in second and early third trimester fetuses (18–31 weeks' gestation) as 0.53 ± 0.13. Their study included 74 cases. Mori et al. reported normal LV TI of 0.35 ± 0.03. Mori and his colleagues did not find any difference in the TI throughout gestation (30). Similarly, Eidem et al. demonstrated the fetal LV TI to be 0.35 ± 0.03 with no change during gestation (10).

Cruz-Martinez et al., had the largest cohort before our study. They had a total of 730 fetuses. They showed a progressive increase in the mean MPI from 11 weeks (mean, 0.39; 95th centile, 0.51) to 41 weeks (mean, 0.55; 95th centile, 0.78) of gestation [36]. Our Mod MPI values are very similar to Cruz-Martinez et al. results from 20 weeks till 32 weeks gestational age (Fig. 6). Their values tend to increase from 33 weeks till 41 weeks and the ranges widens from 33 weeks till 41 weeks gestational age. Both studies used similar techniques to obtain Mod MPI. This strengthens the idea, that using the same techniques results are very similar. Both studies did not include diverse ethnicities (Fig. 7).

Maheshwari et al. gave a detailed analysis of different technique and proposed an automated system of Mod-MPI measurement, however, there was no automated measurement of MPI to the best of our knowledge yet. There [KA1] is conflicting evidence whether Mod MPI is useful in fetal growth restriction. Looking at recent

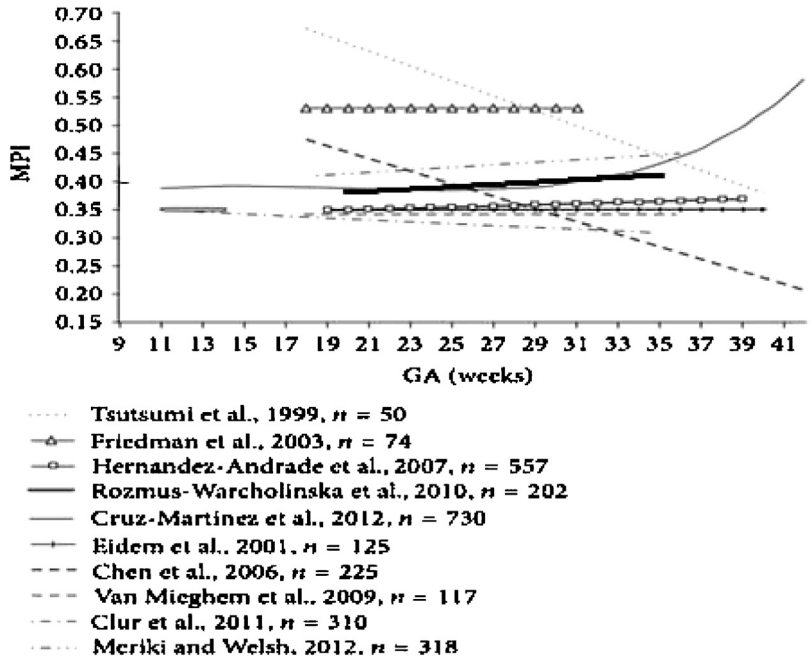

Fig. 7. GA-adjusted mean values for fetal left Mod MPI in our studies (bold black line) with plotted data compared to published values from 1999. Adapted from Cruz-Martinez et al, 2012.

studies that compared Mod MPI with fetal Dopplers in fetal growth restriction, we can note Zhang et al [41] who checked 177 early and late growth restricted foetuses. Zhang et al showed that growth restricted fetuses had increased MOD MPI. On the other hand, Henry et al. [42] compared 52 small for gestational age foetuses with 100 controls. Henry et al. concluded that MOD MPI did not demonstrate clinical utility in management of fetal growth restriction [43].

Strengths and limitations

Strengths of our study include: first, a large population of women undergoing routine ultrasound examination in pregnancy. Second, all scans were performed by trained sonographers who carried out the measurements according to a standardized protocol; and third, examination of factors from maternal characteristics that affect the measurements. In the establishment of normal reference ranges, we included all pregnancies undergoing routine ultrasound examination but excluded those with pre exiting medical conditions or pregnancy complication.

The significant limitation of our study was the lack of an invasive gold standard of assessing global myocardial function in the fetus to compare with our non-invasive measurements. In addition, our study group was cross-sectional study. We only assessed LV myocardial function in our study and did not comment on RV myocardial performance.

Conclusion

In our study, we demonstrated that the measurements of the ICT, IRT and ET are easily obtained in the fetus during the gestational time period. Mod MPI was calculated by easily plotting of start and end points on the ultrasound machine.

Normal values for Mod MPI were established in our study. Also, graph with 10th and 90th centiles were generated. Our data are similar to those of other groups who have assessed LV myocardial performance with slight differences. In addition, we found that the Mod MPI appeared to be independent of GA within the gestational age group we evaluated. Maternal age, parity and BMI does not seem to affect Mod MPI value.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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