Current Cardiology Reviews, 2022, *18*, e271221199505

MINI-REVIEW ARTICLE

Fetal Cardiac Function: Myocardial Performance Index

Mariana Oliveira[1,*], Joana Portela Dias[1,2,3] and Luís Guedes-Martins[1,2,3,4]

[1]*Instituto de Ciências Biomédicas Abel Salazar, University of Porto, 4050-313 Porto, Portugal;* [2]*Departamento da Mulher e da Medicina Reprodutiva, Centro Materno Infantil do Norte, Centro Hospitalar do Porto EPE, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal;* [3]*Unidade de Investigação e Formação, Centro Materno Infantil do Norte, 4099-001 Porto, Portugal;* [4]*Instituto de Investigação e Inovação em Saúde, Universidade do Porto, 4200-319 Porto, Portugal*

ARTICLE HISTORY

Received: September 02, 2021
Revised: October 15, 2021
Accepted: November 05, 2021

DOI:
10.2174/1573403X18666211227145856

Abstract: The Myocardial Performance Index (MPI) or Tei index, presented by Tei in 1995, is the ratio of the sum of the duration of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) to the duration of the ejection time (ET). The Modified Myocardial Performance Index (Mod-MPI), proposed in 2005, is considered a reliable and useful tool in the study of fetal heart function in several conditions, such as growth restriction, twin-twin transfusion syndrome, maternal diabetes, preeclampsia, intrahepatic cholestasis of pregnancy, and adverse perinatal outcomes. Nevertheless, clinical translation is currently limited by poorly standardised methodology as variations in the technique, machine settings, caliper placement, and specific training required can result in significantly different MPI values. This review aims to provide a survey of the relevant literature on MPI, present a strict methodology and technical considerations, and propose future research.

Keywords: Fetal heart, doppler, fetal echocardiography, fetal myocardial performance index, Tei index, heart function.

1. INTRODUCTION

Normal cardiac function implies preserved systolic and diastolic performance and synchronized cardiac time periods [1, 2].

Primary cardiovascular and systemic disorders may influence the fetal heart [3]. The incidence of congenital heart disease is high [4], and fetal surveillance includes more sensitive markers than just fetal heart rate monitoring [5]. A broad range of ultrasonography techniques to evaluate structural and functional abnormalities can be used, particularly Doppler ultrasound for hemodynamic assessment [2, 6, 7]. Doppler imaging can reflect myocardial motion by measuring myocardial velocities [8] and can be used in pregnancy to determine normal physiologic [9] and underlying pathophysiologic characteristics [10, 11].

The advances in this technology have resulted in providing enhanced imagery of the fetal heart, which is particularly noticeable during/in the first trimester [11]. For this reason, these improvements represent important achievements in matters related to fetal intervention, time of delivery, and other managerial decisions [12]. Early diagnosis of cardiac defects allows families to prepare for the birth of a sick child. Distinctly, this helps in reducing the anxiety of high-risk patients who have a previous family history of cardiac defects [4, 13].

* Address correspondence to this author at the Instituto de Ciências Biomédicas Abel Salazar, University of Porto, 4050-313 Porto, Portugal; Tel: +351918524121; E-mail:marianaduquefo@gmail.com

However, as Doppler imaging was first designed to evaluate the adult heart as an early tool to evaluate cardiac dysfunction and to predict mortality and morbidity associated with cardiovascular disease, its application to the fetus has some limitations such as a variable position, fetal and respiratory movements, a higher heart rate and the fact that simultaneous ECG cannot be easily performed [10].

The Myocardial Performance Index (MPI) or Tei index, presented by Tei in 1995 [6], is the ratio of the sum of the duration of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) to the duration of the ejection time (ET) [4, 5, 14-16]. It can also be defined as (a-b)/b, where 'a' is the interval between the end and the onset of systemic ventricular inflow, and 'b' is the ejection time of the systemic outflow [9].

The ICT is the period between the closure of the atrioventricular valves and the aperture of the semilunar valves (important for the assessment of systolic function). The IRT is the period between the closure of the semilunar valves and the aperture of the atrioventricular valves (important for diastolic function). The ET starts when the semilunar valves open and ends when these valves close [2, 5, 7].

MPI is a potentially useful predictor of global cardiac function, which is not influenced by heart size, shape, orientation, geometry, or rate [3, 17, 18]. Its application in the fetus has advantages over the application in adults since it is possible to measure the atrioventricular and semilunar valve flows simultaneously, removing the inaccuracy predisposed in measuring different heartbeats [4].

1875-6557/22 $65.00+.00

In 2005, Modified Myocardial Performance Index (Mod-MPI) was proposed to clearly define the time intervals using the Doppler valve clicks [19, 20]. The Mod-MPI is considered a reliable and useful tool in the study of fetal heart function in several conditions, such as intrauterine growth restriction, preeclampsia, maternal diabetes, congenital heart malformations, and twin-to-twin transfusion syndrome or through different pathophysiological states that include hypoxia, metabolic acidosis, and increased fetal cardiac afterload [2, 8, 12, 13, 18, 20].

Nevertheless, clinical translation is currently limited by poorly standardised methodology as variations in the technique, machine settings, caliper placement, and specific training required can result in significantly different Mod-MPI values [2, 12]. To evaluate if this method can be clinically useful, greater development is needed to differentiate between normal and abnormal MPI values in different fetal pathological conditions [8].

Different studies show that automated analysis diminishes the subjectivity in the definition of cardiac time intervals, has superior reproducibility over manual measurements and can facilitate the application of MPI [12, 14, 19].

In this review, we provide a survey of the relevant literature on MPI in fetal cardiology, present technical considerations, and suggest future research.

2. METHODS

To compose this review, thorough literature searches were repeatedly conducted in PubMed and Medline. However, a limitation of articles written in the English language was observed. The search terms used were fetal heart, doppler, fetal echocardiography, fetal myocardial performance index, and heart function. The references of all analysed studies were searched to obtain the necessary information. Additionally, we devised a table covering the most relevant topics within this review.

3. ACQUISITION OF MPI IN FETAL ECHOCARDIOGRAPHY

Left MPI is determined by obtaining the transverse four or five-chamber view with an apical or bottom heart [21, 22] and placing the sample volume simultaneously near the mitral inflow and aorta outflow on the spectral Doppler [23]. The recording of both isovolumetric periods and ejection time together within the same cardiac cycle is possible due to the small size of the fetal cardiac chambers and the proximity of mitral inflow and aortic outflow [2]. MPI is then calculated as (ICT+IRT)/ET [21].

The ideal images should be obtained in the absence of fetal movements and with the suspension of maternal respiration, which may make the sample volume placement difficult [2]. Three successive measurements, including all the intervals, should be performed [2, 22].

Right MPI is a feasible reflection of fetal cardiac function because the fetal heart is physiologically right-side dominant [12]. With the heart maturation, after 20 weeks of gestation, the tricuspid and pulmonary valves are in different anatomical planes, so two waveforms from two different cardiac cycles are necessary [19, 24]. Therefore, the methodology is more technical and time-consuming and introduces sources of possible variation [19]. During the recordings, machine settings must be kept constant, and fetal heart rate should differ by a maximum of 10 beats/min [2]. To measure the tricuspid and pulmonary flows, the sample volume can be placed over the tricuspid and pulmonary valve in an apical or basal four-chamber view and a short-axis view or a sagittal plane, respectively [2, 19]. It can be calculated by the formula (a-b)/b [19]. The 'a' is measured from the closure click to the aperture click of the tricuspid valve, and the 'b'(right ventricular ET) is measured from the aperture click to the closure click of the pulmonary valve [2].

The click of the opening of the aortic valve was used to define the limits of the ejection period by Raboisson *et al.* [3]. Later, Hernandez-Andrade E *et al.* developed the use of the mitral valve closing click and clearly defined the three-time intervals by visualizing the clicks of both valves (Mod-MPI) (Fig. **1**) [3, 7, 12].

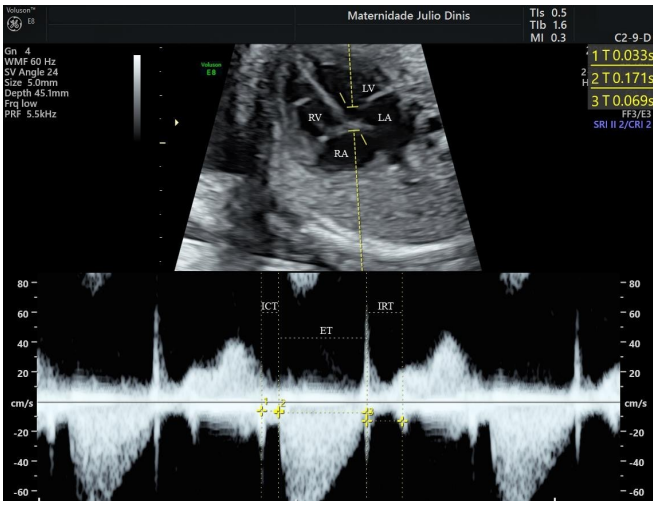

Fig. (1). Mod-MPI Doppler waveform showing the time intervals (ICT, IRT and ET).

Several studies have used the method recommended by Hernandez-Andrade E *et al.* for the Mod-MPI measurement by placing the sample volume near the lateral wall of the ascending aorta below the aortic valve and just above the mitral valve on a transverse four-chamber view [2, 6, 12, 16, 18, 21, 23, 25-28].

Values can be affected by ultrasound machine settings as caliper placement, sample volume (SV), angle of insonation (AI), Doppler sweep velocity (DSV), wall motion filter (WMF), and Doppler gain (DG). To minimize this variability, strict criteria should be applied [26]. Also, the use of the same ultrasound equipment during patient follow-up and specific reference ranges for each ultrasound system is recommended [2, 23].

With reference to the calliper placement, the opening and closing of valve leaflets produce "original" clicks in the same direction as blood flow for opening clicks, or in the opposite direction, for closing clicks. It is possible that smaller echoes may be present in the opposite direction to the original clicks ("reflected" clicks). There is a common peak time point for original and reflected clicks, and it is suggested that more precise measurement is achieved with thinner clicks. The calliper can be placed at the beginning, from the end to the beginning of the valve clicks (corresponding to physiological time intervals), and at the peak or end of the valve clicks [2, 15, 24].

Meriki *et al.* described as optimal settings the SV of 3 mm, the AI <30°, the fastest possible DSV to create greater horizontal stretch and valve clicks visualization (15 cm/s in this case), the lowest DG to clearly visualize echoes corresponding to valve clicks [15], high-pass WMF (in this case 70 Hz) to omit slow blood motion (artefacts) signals and to get a clear demarcation of time intervals [15] and the placement of the calliper at the beginning of valve clicks [2, 24].

Meriki *et al.* showed further refinements with improved repeatability and a fixed WMF at 300 Hz, and stated that the angle of insonation should be kept less than 15°, Doppler aliasing should be avoided, and the measurement should be at the peak of valve clicks [20].

Lobmaier *et al.* have investigated differing ultrasound settings and equipment (Siemen Antares and Voluson 730 Expert) and their impact on left Mod-MPI values. The conclusion was that raised DSV and WMF resulted in superior measurement repeatability [24].

Some other studies have used the standardized method of decreasing DG, using the fastest DSV, increasing the WMF, and using an AI close to 0° with a maximum of 15° [12, 26, 27], 20° [23] or 30° [2, 18].

MPI can be measured in both manual and automatic ways. Manual measurement is time-consuming and requires experience to analyse the waveform in the context of a fetal cardiac cycle and perform the correct identification of the valve clicks. To produce reliable measurements, an average of 65 fetal MPI measurements is required [16, 24].

Automated models have already been developed and can remove the need for training, although experience is still required to acquire the correct Doppler waveform successfully [19, 29].

An Auto Mod-MPI system (Samsung Electronics Co. Ltd., Suwon, South Korea) was proposed by Lee *et al.* It detects valve clicks using a methodology that requires the operator to manually select a region of interest in the Doppler waveform before any upcoming image analysis can occur [24, 27].

Maheshwari *et al.* have developed a novel automated MPI system that automatically locates valve click peaks and calculates the Mod-MPI [24].

Tissue Doppler imaging (TDI) has also been proposed to measure the MPI. Both spectral and colour TDI can be used [2].

Systolic (S′), early diastolic (E′), and late diastolic or atrial (A′) myocardial velocity waveforms can be obtained in the same timeline. Left, right, and septal MPI' (Tissue Doppler MPI) can be calculated as (ICT' + IRT')/ET' in which ICT' is from the end of A' to the beginning of S', IRT' is from the end of S' to the beginning of E' and ET' from the beginning to the end of S' [2]. It is possible that the TDI method may be more sensitive, has less variability and more precision than conventional MPI [6, 10].

4. REFERENCE RANGES OF MYOCARDIAL PERFORMANCE INDEX

The difficulty in the clinical application of MPI is based on the absence of standardized measurement, the lack of clarity regarding the relationship of the cardiac function with advancing gestational age (GA), and the variations in normal reference values (Table **1**). The 20 studies in the table try to define reference ranges including LV MPI, RV MPI, LV Mod-MPI, LV MPI' or RV MPI' values depending on each article. GA varies from 11 to 40 weeks.

Table 1. Comparison of different studies reporting normal reference values for the MPI, Mod-MPI, and MPI' according to gestational age.

Date/Ref	Objective	Type of Study	Sample Size	Gestional Age	Variation Found	
2019 [23]	To determine reference ranges for the E wave, A wave, E/A ratio, and LV Mod-MPI.	Prospective cross-sectional study	360	20-36+6 weeks	LV Mod-MPI [0.44; 0.47]	Increasing trend with the GA.
2018 [30]	To describe the longitudinal changes of fetal MPI of uncomplicated monochorionic diamniotic twin.	Longitudinal study	83	17-26 weeks	LV MPI [0.274; 0.570]	Increasing trend with the GA.
					RV MPI [0.304; 0.557]	
					LV MPI' [0.350; 0.643]	
					RV MPI' [0.398; 0.632]	

(Table 1) contd....

Date/Ref	Objective	Type of Study	Sample Size	Gestional Age	Variation Found	
2017 [12]	To compare fetal left Mod-MPI values to published reference ranges.	Prospective longitudinal study	265	27-29 weeks	LV Mod-MPI [0.51; 0.53]	Increasing trend with the GA.
			254	35-37 weeks	LV Mod-MPI [0.52; 0.54]	
2017 [19]	To compare the repeatability and degree of absolute agreement of an automated fetal RV MPI algorithm with manual measurements.	Prospective cross-sectional study	65	22-39 weeks	RV MPI [0.58±0.10]	Non specified trend.
2016 [31]	To construct biventricular reference ranges for ICT, IRT, and ET for cTDI.	Prospective cross-sectional study	160	15-37 weeks	RV MPI' [0.538±0.117] LV MPI' [0.544±0.118]	Constant throughout gestation.
2016 [26]	To establish normal reference ranges for left Mod-MPI measured by the Auto Mod-MPI system and evaluate Mod-MPI changes in recipients of twin- to-twin transfusion syndrome (TTTS) before and after fetoscopic laser coagulation.	Prospective longitudinal study	222	12-40 weeks	LV Mod-MPI [0.44; 0.56]	Increasing trend with the GA.
2014 [33]	To establish gestational age-adjusted reference intervals and trends of Mod-MPI, ICT, IRT, and ET in pregnancy.	Transversal study	419	20-38 weeks	LV Mod-MPI [0.32; 0.42]	Constant from 20 to 26weeks and decreasing with advancing GA.
2014 [6]	To establish reference ranges of fetal MPI in normal singleton pregnancies.	Prospective longitudinal study	562	12-40 weeks	LV Mod-MPI [0.31; 0.71]	Increasing trend with the GA.
2013 [3]	To elucidate normal values of LV and RV MPI values in second and third-trimester fetuses and compare these values with other previously published data.	Retrospective longitudinal study	420 230	2nd trimester	LV MPI [0.464±0.08]	Independent of GA.
			190	3rd trimester		
			150	2nd trimester	RV MPI [0.466±0.09]	
			100	3rd trimester		
2012 [28]	To establish normal reference intervals of the fetal left Mod-MPI with the use of stringent criteria for delimitation of the time periods.	Transversal study	730	11-41 weeks	LV Mod-MPI [0.29; 0.78]	Increasing from 34 to 41 weeks.
2012 [32]	To construct gestational age-adjusted reference ranges of the left fetal Mod-MPI in the Australian population and assess the influence of valve click caliper position on constituent time intervals and the Mod-MPI.	Prospective longitudinal study	117	18-38 weeks	LV Mod-MPI [0.50±0.08] (caliper position: original peak click)	Increasing trend with the GA.
					LV Mod-MPI [0.42±0.07] (caliper position: reflected peak click)	
					LV Mod-MPI [0.42±0.07] (caliper position: peak click)	
2011 [33]	To determine if, in fetuses with normal hearts, the NT thickness is related to cardiac function throughout gestation.	Prospective longitudinal study	120	11-15 weeks	RV MPI [0.35 ± 0.14] LV MPI [0.36 ± 0.12]	Non specified trend.
			98	18-22 weeks	RV MPI [0.32 ± 0.16] LV MPI [0.31 ± 0.12]	
			35	28-32 weeks	RV MPI [0.35 ± 0.22] LV MPI [0.31 ± 0.15]	
2011 [34]	To construct gestational age (GA)- and estimated fetal weight (EFW)-adjusted reference ranges for tissue Doppler cardiac function parameters.	Prospective cross-sectional study	213	24-41 weeks	Left MPI' [0.435 + (0.0003 ×GA)±0.0858]	Constant throughout gestation.
					Right MPI' [0.4943±0.0793]	
					Septal MPI' [0.5098±0.0683]	

(Table 1) contd....

Date/Ref	Objective	Type of Study	Sample Size	Gestional Age	Variation Found	
2010 [35]	To evaluate the fetal cardiocirculatory dynamics during routine first-trimester screening and establish cross-sectional reference ranges.	Prospective cross-sectional study	202	11-14 weeks	LV MPI [0.375±0.092] RV MPI [0.332±0.079]	Constant throughout gestation.
2008 [36]	To test the validity of the MPI and its components against the more conventional methods of fetal cardiac function assessment: the ejection fraction (EF) for systolic function and the E/A index (ratio of transmitral flow during early (E) ventricular filling to flow during atrial (A) contraction) for diastolic function, both in a normal population and in a population at risk for cardiac failure because of volume overload (recipient fetuses in cases of twin-twin transfusion syndrome (TTTS)).	Prospective cross-sectional study	117	20-36 weeks	LV MPI [0.34±0.05]	Independent of GA.
2007 [37]	To construct normal reference values for the Mod-MPI.	Transversal study	557	19-39 weeks	LV Mod-MPI [0,28; 0,45]	Increasing trend with the GA.
2006 [38]	To define the value of the Tei index of normal fetuses and to estimate the influence of gestational week and heart rate on the index.	Prospective longitudinal study	225	18-27+6 weeks	LV MPI [0.37±0.08] RV MPI [0.39±0.04]	Decreasing trend with the GA.
				28-36+6 weeks	LV MPI [0.27±0.05] RV MPI [0.30±0.05]	
				37-42 weeks	LV MPI [0.22±0.05] RV MPI [0.24±0.04]	
2003 [22]	To determine normal values of fetal LV Tei Index in second and third-trimester fetuses and to compare these to other values reported in the literature.	Prospective cross-sectional study	74	18-31 weeks	LV MPI [0.53±0.13]	Independent of GA.
2001 [39]	To define the MPI in a group of normal fetuses and compare these data to other published studies of this index.	Retrospective longitudinal study	125	20-40 weeks	LV MPI [0.36±0.06] RV MPI [0.35±0.05]	Constant throughout gestation.
1999 [40]	To assess physiologic changes of global ventricular function determined by Tei index in fetuses during the second and the third trimester of pregnancy and in neonates during their transition to postnatal circulation, to examine the Tei index in fetuses with intrauterine growth retardation (IUGR) and fetuses of diabetic mothers (DM).	Prospective longitudinal study	50	18-26 weeks	RV MPI [0.62±0.06] LV MPI [0.62±0.07]	Decreasing trend with the GA.
				27-33 weeks	LV MPI [0.51±0.04] RV MPI [0.53±0.04]	
				34-40 weeks	LV MPI [0.43±0.03] RV MPI [0.49±0.05]	

The minimum and maximum values reported for LV MPI are 0.16 [33] and 0,69 [40], respectively, and for RV MPI are 0,16 [33] and 0,68 [19, 40], respectively. In the case of LV Mod-MPI, the minimum and maximum values are 0,28 [37] and 0,78 [28], respectively.

MPI' has been described in 3 articles, with the minimum and maximum values for LV MPI' being 0,350 [30] and 0,662 [31] and for RV MPI' 0,398 [30] and 0,655 [31], respectively. The minimum and maximum variations found for the same parameter in the same study were 0,02 [12] and 0,49 [28].

As exposed above, there is a lack of consensus on the reference curves since the variation found in the different studies of the literature is remarkable. Two of the studies have not specified an MPI variation trend [19, 33]. Two MPI studies [35, 39] and two MPI' studies [31, 34] have shown that the values remain constant with advancing GA. Another three MPI studies found that MPI is independent of GA [3, 22, 36]. A study indicated that Mod-MPI remains constant from 20 to 26 weeks and decreases with advancing GA [18]. A decrease in MPI with advancing GA was found in two other studies [38, 40].

The most frequent variation trend was the increase in the values with advancing GA. One study reported an increase in MPI with advancing GA [30], and there were seven studies that noticed an increase in Mod-MPI with advancing GA [6, 12, 23, 26, 28, 32, 37]. Besides, the studies with greater power (larger sample sizes) described this increasing trend [6, 28, 37].

It is noteworthy to mention that one study showed a better inter-observer correlation in a group between 35 and 37 weeks of gestation when compared to a 27 to 29 weeks group, suggesting that measurements may be more reliable and reproducible later in pregnancy [12].

5. ASSESSMENT OF MYOCARDIAL PERFORMANCE INDEX IN FETUSES WITH GROWTH RESTRICTION

Intrauterine growth restriction (IUGR) designates a pathological condition in small-for-gestational age (SGA) fetuses [41-43].

The most common cause is placental insufficiency which results in chronic hypoxia and volume/pressure overload, triggering an adaptive response on the fetus that includes an arterial redistribution where the blood flow is redirected to the brain and the heart [41, 44-46].

Some authors have described subsequent alterations in the cardiac geometry and shape, such as a spherical shape resultant of ventricular dilation rather than increasing myocardial hypertrophy [41]. This situation leads to systolic and/or diastolic dysfunction that presents with lower cardiac compliance, lower peak velocities in the aorta and pulmonary arteries, increased aortic and decreased pulmonary time to peak velocity, increased arterial stiffness, increased cardiac afterload, and a relative increase in left cardiac output associated with decreased right cardiac output and end-diastolic ventricular filling [41, 44, 47].

Fetal cardiac dysfunction could also derive from direct repercussions of IUGR hypoxemia and hypoglycaemia on myocardial contractility and from the polycythemia that increases blood viscosity and alters preload [45]. These mechanisms of cardiac adaptation are known as cardiac remodeling [44].

A higher MPI was presented in SGA fetuses when compared to appropriate-for-gestational age (AGA) fetuses [43, 48]. The Doppler study of the umbilical artery (UA) flow is the clinical standard to differentiate between constitutional SGA and IUGR; however, some studies have questioned its effectiveness. Even in SGA fetuses with normal UA Doppler, significant differences in cardiac function parameters were found, including MPI, reflecting late-onset forms of IUGR [48-50].

An elevated MPI has been reported in IUGR fetuses [40, 44, 47, 51-53] and newborns [41, 46]. A few studies have not found a significant difference between both the groups [42, 54, 55].

In animals, a good model to mimic haemodynamic IUGR features of human fetuses is the selective ligature of uteroplacental vessels, although a study in rabbits could only show a non-significant trend for increased MPI values [56].

Some studies demonstrate that MPI increases throughout the deterioration stages [47, 53]. It has been used as one of the earliest cardiac dysfunction markers in intrauterine life, showing an association with biochemical markers (atrial and B-type natriuretic peptides) as IUGR advances [41, 48, 53, 57, 58]. Regarding monochorionic diamniotic twins, although there is limited available data regarding longitudinal MPI in selective IUGR (sIUGR) or pregnancy outcome prediction, MPI could be a potential evaluation technique if used by experienced ultrasonographers [59].

In co-existing preeclampsia and IUGR pregnancies, there is a fetal cardiac function aggravation, and MPI tracking could enable better monitoring [59]. Abnormal MPI in IUGR is also associated with adverse perinatal outcomes, including increased morbidity and death [45, 47, 53, 60]. Thus, MPI is an important evaluation tool for suspected IUGR, preventing adverse short and long-term outcomes [47].

6. ASSESSMENT OF MYOCARDIAL PERFORMANCE INDEX IN TWIN-TWIN TRANSFUSION SYNDROME

Twin-twin transfusion syndrome (TTTS) is a serious condition present in 10 to 15% of monochorionic twin pregnancies [61].

Ultrasonography is the method for diagnosis and evaluation of the TTTS severity, allowing its staging through the Quintero system [62, 63]. However, cardiac dysfunction is not taken into account in this system and may be present in the early stages of the disease [57, 62-66].

In fact, some indices like LV-MPI', RV-MPI and LV-MPI appeared to be significantly elevated in future TTTS recipients, while RV-MPI' was detectably lower in donors before the diagnosis [66].

A study found that in cases where there is only liquor and/or growth discordance at presentation, not meeting criteria for any specific disease, MPI might be useful in predicting which cases will advance to TTTS [57].

Selective laser photocoagulation of communicating vessels (SLPCV) is the treatment of choice and substantially enhances survival rates, leading to extreme hemodynamic changes in both twins [57, 61]. The fetus' adaptive capacities and the myocardial status before surgery influence the cardiac response [63].

On the other hand, MPI and MPI′ demonstrate cardiac dysfunction in TTTS and improve after this treatment [30].

An automated analysis study of recipient twins determined an abnormal Mod-MPI in the majority of them [26]. A study presented higher MPI values in both donors and recipients at all severity stages when compared to uncomplicated monochorionic twins. This happens due to different changes in the time intervals: prolonged ICT and IRT in re-

cipients and shortened ET in donors [26], probably reflecting the state of hypervolemia and pressure overload and hypovolemia, respectively. These changes partially improved 72 hours after the SLPCV [61].

A study that tested recipient myocardial performance in the pre-, intra-, and post-operative periods showed that MPI worsens during the intra-operative period before returning to pre-operative levels in 12-24 hours. The right-sided Tei index was found to reduce more than 24 hours after the procedure [67]. A different study found that an increase in pre-operative recipient RV-MPI was associated with decreased survival at 30 days [64]. Other studies reported a substantial improvement in recipient LV [63, 65] and RV [66] MPI postoperatively.

7. ASSESSMENT OF MYOCARDIAL PERFORMANCE INDEX AND DIABETES

Contrary to TTTS, fetal complications in both Gestational Diabetes Mellitus (GDM) and Pregestational Diabetic pregnancies (PDP) are not related to placental insufficiency but to fetal hyperinsulinism and resultant abnormal metabolic status [68].

Fetal findings are myocardial hypertrophy with thickening of the interventricular septum and impaired ventricular compliance, increased preload index, culminating in diastolic and systolic dysfunction [68-71].

In PDP fetuses, MPI can evince early cardiac function alterations preceding the structural changes [72, 73]. In fact, a higher fetal MPI [69-71, 73-75] and MPI' [76] can be seen in GDM and PDP when compared to non-diabetic pregnancies.

MPI was increased in poorly controlled diabetics [73, 75, 77] as well as in well-controlled diabetics [70, 72] compared to healthy pregnancies.

Additionally, two studies found that this increase is independent of the onset of DM (pregestational vs. gestational) [71, 74]. One of them revealed a decrease in ET, especially in the pregestational group [71]. Also, the requirement of insulin for glycemic control was reflected in a higher Mod-MPI in comparison with those requiring diet alone [71].

In a study concerning the perinatal outcome, it was found that in diabetic pregnancies, adverse outcomes were correlated with a higher MPI when compared with normal outcomes [70].

A study reported a left ventricular MPI value > 0.52 for the prediction of adverse perinatal outcomes [77]. A different study appointed MPI as a better predictor in the second trimester [72].

Two studies reported a higher MPI in fetuses with gestational impaired glucose tolerance (GIGT) with an adverse outcome [68, 70]. Surprisingly, a study in fetuses of women with mild GIGT showed lower left and right MPI in late gestation [78].

A study revealed that TDI MPI is more sensitive than spectral Doppler MPI in PDP [79].

8. ASSESSMENT OF MYOCARDIAL PERFORMANCE INDEX AND PREECLAMPSIA

Preeclampsia (PE) is a placental-mediated disease, expressing placental maladaptation and lack of vascular remodelling of the spiral arterioles. This induces increased placental vascular resistance and increased fetal cardiac afterload, affecting cardiac function [51, 80].

Three studies found a higher MPI in pregnancies complicated by PE compared to non-complicated ones [51, 59, 80]. On the other hand, two studies suggested that PE per se does not have an impact on the MPI value [81, 82].

A study showed cardiac dysfunction with similar MPI values in fetuses with preeclamptic mothers, independently of their growth, though with a different pattern. A prolonged ICT in normally grown fetuses reflects systolic dysfunction, while a decreased ET and prolonged IRT reflect both systolic and diastolic dysfunction in fetuses with growth restriction [83]. Another study showed a higher median Mod-MPI value (due to all its components) in the PE+IUGR group [59].

A study concerning mild/stable placental-mediated disease (including mild preeclampsia) has shown that a single elevated MPI can be a good predictor of adverse neonatal outcomes. The highest number of adverse outcomes was documented in the PE+IUGR group [51]. A cut-off Mod-MPI value ≥ 0.55 was suggested for adverse perinatal outcomes [59].

9. ASSESSMENT OF MYOCARDIAL PERFORMANCE INDEX AND INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Although considerably benign to women, intrahepatic cholestasis of pregnancy (ICP) may have serious consequences for the fetus, an identified cause of sudden intrauterine fetal death [84, 85].

The presence of elevated maternal serum bile acid (SBA) levels may affect the fetal heart. Animal studies suggest abnormal cardiomyocyte contraction and conduction caused by a toxic effect of bile acids [85, 86].

In fact, three studies demonstrated increased LV MPI values in fetuses affected by ICP [84-86]. Two of them registered an increase in both ICT and IRT components [84, 85].

A study has shown a positive correlation between LV MPI and increasing maternal SBA levels [85]; yet, a different study did not find any correlation [84].

In what concerns the severity of the disease, two studies did not find significant LV MPI differences between mild and severe ICP cases [84, 85].

In these cases, evidence for the use of LV MPI in the prediction of adverse perinatal outcomes has been found. A study suggested a cut-off value of MPI > 0.48 [84, 86].

10. ASSESSMENT OF MYOCARDIAL PERFORMANCE INDEX AND ADVERSE PERINATAL OUTCOME

In most cases, there is an association between the elevation of MPI and increased adverse perinatal outcomes. It appears to be an adverse outcome predictor in IUGR, TTTS, maternal diabetes, persistent pulmonary hypertension of the newborn (PPHN), and indirectly, in ICP.

In IUGR cases, the more severe the grade, the worse the outcomes are. MPI is considered a significant predictor of adverse outcomes [47, 60]. A cut-off MPI value of ≥0.54 for an adverse outcome and a cut-off MPI value of ≥0.67 for perinatal death have been proposed. Adverse outcomes include perinatal death, neonatal resuscitation, hypoxic-ischemic encephalopathy, neonatal pH < 7.15, intraventricular haemorrhage, and bronchopulmonary dysplasia [47]. A study proposed a combination of DV flow with MPI for a better predictive probability than any single parameter [60]. A study with early-onset IUGR fetuses also showed that MPI has an individual predictive value for perinatal mortality [87]. In what concerns TTTS lower stages, MPI values are considered predictors of recipient fetus loss. Furthermore, a higher risk of loss of at least one of the twins displayed an increased MPI [88]. SLPCV in TTTS cases substantially enhances survival rates and was associated with recipients' postoperative RVMPI reduction in more severe cases in one study and with recipients' LVMPI reduction in another [61, 63, 89]. One study showed an association between abnormal UA doppler and RVMPI with a high risk of post-SLPCV fetal demise [90]. On the other hand, a study presented no clear association between MPI and fetal death after laser surgery [91].

In the case of single fetal death (FD) in a monochorionic twin pregnancy (MCTP), the surviving fetus showed the maximum value of LV and RV MPI at the time of the confirmation of the single FD. Intrauterine transfusion (IUT) may prevent poor perinatal outcomes; the majority of co-twins of a single FD in an MCTP with superficial anastomoses exhibited poor outcomes. The recipients' MPI decreased promptly after this procedure and cardiac function was found to be normal after birth [92].

In studies concerning diabetic mothers, MPI was elevated in the group with adverse outcomes and served as an independent predictor of adverse outcomes [70, 77]. A cut-off value ≥ 0,52 was proposed [77]. The main adverse outcomes were low Apgars, hypoglycaemia, polycythaemia, low pH, perinatal death, admission to the neonatal intensive care unit, cord pH <7.15, and the presence of cardiomyopathy [70, 77]. MPI was presented as an excellent predictor of adverse outcome in the GIGT group, showing elevated MPI when compared to fetuses with normal outcomes [68].

Regarding ICP, there has been an association observed between high SBA and cholestatic IUFD. A study showed higher LVMPI in fetuses with high SBA values when compared with cholestatic patients with lesser SBA elevation [85].

In a study involving a PPHN group, the LVMPI tended to be higher in cases of adverse outcomes [death or that required ECMO (extracorporeal membrane oxygenation)]. The causes of death were a hypoxemic respiratory failure, an inborn error of metabolism, trisomy, acute renal failure, disseminated herpes simplex viral infection, sepsis, cerebral infarct, intracerebral bleed, and hypoxic-ischemic encephalopathy [93].

11. DISCUSSION

MPI may have a great value as a noninvasive marker of global myocardial function and maybe a sensitive tool for detecting fetal cardiac dysfunction [24]. As it is of accessible applicability, it can serve as an initial fetal cardiac approach, allowing an indication for a complete fetal echocardiographic assessment [2].

To achieve its full potential, a consensus must be reached regarding standardised methodologies, such as variations in the technique, machine settings, calliper placement, and specific training required. Left Mod-MPI should be determined by obtaining the transverse four or five-chamber view with an apical or bottom heart [21, 22] and placing the sample volume simultaneously near the mitral inflow and aorta outflow (lateral wall of the ascending aorta below the aortic valve and just above the mitral valve as recommended by Hernandez-Andrade) on the spectral Doppler [23]. The valve clicks should be used to define the limits of time periods [3].

In general, these optimal settings have been the most suggested: SV of 3mm, the AI <15°, the fastest possible DSV, the lowest DG, high-pass WMF (for example, 300Hz), avoidance of Doppler aliasing, and the placement of the calliper at the beginning of valve clicks [2, 12, 24, 26, 27].

As manual measurement is time-consuming and requires experience (reliable measurements require an average of 65 fetal MPI measurements) [16, 24], automated models may bring advantages [19, 29].

It is possible to measure MPI with TDI, both spectral or colour [2]. In a study concerning PDP, TDI MPI was presented as more sensitive than spectral Doppler MPI [79].

Larger studies with this standardised methodology are needed to formalize normal reference values since there is a vast variation among existing studies. In the case of LV Mod-MPI, the minimum and maximum values are 0,28 [37] and 0,78 [28], respectively, which makes clinical application strenuous.

The increase of Mod-MPI/MPI with advancing GA seems to be the variation trend [6, 12, 23, 26, 28, 30, 32, 37]. To conclude, according to the current literature, MPI appears to be significantly elevated in different pathologies, such as SGA and IUGR, TTTS, PDP and GDM, PE, ICP, and PPHN. Additionally, there is evidence of a correlation between the MPI and an increase in adverse perinatal outcomes. More studies regarding standardised methodology are of great significance.

CONCLUSION

As shown above, MPI elevations have been evidenced in different pathologic statuses that affect the fetal systolic and diastolic cardiac functions. These results reinforce its clinical relevance once a demarcation of reference values of normality is achieved. It is quite important to diagnose these pathologies and conduct real-time evaluations of high-risk pregnancies during the maturation and development of the fetus.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

M.O., J.P.D., and L.G-M designed the study. L.G-M. carried out the supervision. M.O., J.P.D., L.G-M. conducted literature review, while critical review has been done by L.G-M. M.O., J.P.D., and L.G-M. contributed to the writing of the manuscript.

REFERENCES

[1] Crispi F, Gratacós E. Fetal cardiac function: Technical considerations and potential research and clinical applications. Fetal Diagn Ther 2012; 32(1-2): 47-64. http://dx.doi.org/10.1159/000338003

[2] Mahajan A, Henry A, Meriki N, *et al.* The (Pulsed- Wave) doppler fetal myocardial performance index: Technical challenges, clinical applications and future research. Fetal Diagn Ther 2015; 38(1): 1-13. http://dx.doi.org/10.1159/000363181

[3] Raboisson MJ, Bourdages M, Fouron JC. Measuring left ventricular myocardial performance index in fetuses. Am J Cardiol 2003; 91: 919-21.

[4] Godfrey ME, Messing B, Cohen SM, Valsky DV, Yagel S. Functional assessment of the fetal heart: A review. Ultrasound Obstet Gynecol 2012; 39(2): 131-44. http://dx.doi.org/10.1002/uog.9064

[5] Khandoker AH, Marzbanrad F, Kimura Y, Al Nuaimi S, Palaniswami M. Assessing the development of fetal myocardial function by a novel doppler myocardial performance index. Conf Proc IEEE Eng Med Biol Soc 2016; 2016: 3753-6. http://dx.doi.org/10.1109/EMBC.2016.7591544 PMID: 28324997

[6] Luewan S, Tongprasert F, Srisupundit K, Traisrisilp K, Tongsong T. Reference ranges of myocardial performance index from 12 to 40 weeks of gestation. Arch Gynecol Obstet 2014; 290(5): 859-65. http://dx.doi.org/10.1007/s00404-014-3288-3 PMID: 24890808

[7] Hernandez-Andrade E, Benavides-Serralde JA, Cruz-Martinez R, Welsh A, Mancilla-Ramirez J. Evaluation of conventional doppler fetal cardiac function parameters: E/A ratios, outflow tracts, and myocardial performance index. Fetal Diagn Ther 2012; 32(1-2): 22-9. http://dx.doi.org/10.1159/000330792 PMID: 22677618

[8] Herling L, Johnson J, Ferm-Widlund K, *et al.* Automated analysis of fetal cardiac function using color tissue doppler imaging in second half of normal pregnancy. Ultrasound Obstet Gynecol 2019; 53(3): 348-57. http://dx.doi.org/10.1002/uog.19037 PMID: 29484743

[9] Iwashima S, Sekii K, Ishikawa T, Itou H. Serial change in myocardial tissue Doppler imaging from fetus to neonate. Early Hum Dev 2013; 89(9): 687-92. http://dx.doi.org/10.1016/j.earlhumdev.2013.04.017 PMID: 23707048

[10] Comas M, Crispi F. Assessment of fetal cardiac function using tissue doppler techniques. Fetal Diagn Ther 2012; 32(1-2): 30-8. http://dx.doi.org/10.1159/000335028

[11] Russell NE, McAuliffe FM. First-trimester fetal cardiac function. J Ultrasound Med 2008; 27(3): 379-83. http://dx.doi.org/10.7863/jum.2008.27.3.379 PMID: 18314516

[12] MacDonald TM, Robinson AJ, Walker SP, Hui L. Prospective longitudinal assessment of the fetal left modified myocardial performance index. J Matern Fetal Neonatal Med 2019; 32(5): 760-7. http://dx.doi.org/10.1080/14767058.2017.1391777 PMID: 29020812

[13] Lee MY, Won HS. Technique of fetal echocardiography. Obstet Gynecol Sci 2013; 56(4): 217-26. http://dx.doi.org/10.5468/ogs.2013.56.4.217 PMID: 24328006

[14] Welsh AW, Maheshwari P, Wang J, *et al.* Evaluation of an automated fetal myocardial performance index. Ultrasound Obstet Gynecol 2016; 48(4): 496-503. http://dx.doi.org/10.1002/uog.15770 PMID: 26423314

[15] Meriki N, Welsh AW. Technical considerations for measurement of the fetal left modified myocardial performance index. Fetal Diagn Ther 2012; 31(1): 76-80. http://dx.doi.org/10.1159/000334385 PMID: 22236694

[16] Cruz-Martinez R, Figueras F, Jaramillo JJ, *et al.* Learning curve for doppler measurement of fetal modified myocardial performance index. Ultrasound Obstet Gynecol 2011; 37(2): 158-62. http://dx.doi.org/10.1002/uog.7765 PMID: 20922780

[17] Nair A, Radhakrishnan S. Fetal left ventricular myocardial performance index: Defining normal values for Indian population and a review of literature. Ann Pediatr Cardiol 2016; 9(2): 132-6. http://dx.doi.org/10.4103/0974-2069.177516 PMID: 27212847

[18] Bhorat I, Bagratee J, Reddy T. Gestational age-adjusted trends and reference intervals of the modified myocardial performance index (Mod-MPI) and its components, with its interpretation in the context of established cardiac physiological principles. Prenat Diagn 2014; 34(11): 1031-6. http://dx.doi.org/10.1002/pd.4414 PMID: 24844183

[19] Leung V, Avnet H, Henry A, Wang J, Redmond S, Welsh AW. Automation of the fetal right myocardial performance index to optimise repeatability. Fetal Diagn Ther 2018; 44(1): 28-35. http://dx.doi.org/10.1159/000478928 PMID: 28950258

[20] Meriki N, Izurieta A, Welsh AW. Fetal left modified myocardial performance index: technical refinements in obtaining pulsed-Doppler waveforms. Ultrasound in Obstetrics & Gynecology 2012; 39(4): 421-9. http://dx.doi.org/10.1002/uog.9090 PMID: 21728210

[21] Zhang L, Han J, Zhang N, *et al.* Assessment of fetal modified myocardial performance index in early-onset and late-onset fetal growth restriction. Echocardiography 2019; 36(6): 1159-64. http://dx.doi.org/10.1111/echo.14364 PMID: 31116471

[22] Friedman D, Buyon J, Kim M, Glickstein JS. Fetal cardiac function assessed by doppler myocardial performance index (Tei Index). Ultrasound Obstet Gynecol 2003; 21(1): 33-6. http://dx.doi.org/10.1002/uog.11 PMID: 12528158

[23] Peixoto AB, Bravo-Valenzuela NJM, Martins WP, Mattar R, Moron AF, Araujo Júnior E. Reference ranges for the left ventricle modified myocardial performance index, respective time periods, and atrioventricular peak velocities between 20 and 36 + 6 weeks of gestation. J Matern Fetal Neonatal Med 2019; 1-10. http://dx.doi.org/10.1080/14767058.2019.1609933 PMID: 30999802

[24] Maheshwari P, Henry A, Welsh AW. The fetal modified myocardial performance index: Is automation the future? Biomed Res Int 2015; 215910. http://dx.doi.org/10.1155/2015/215910 PMID: 26185751

[25] Maheshwari P, Alphonse J, Henry A, Wang J, Redmond SJ, Welsh AW. Beat-to-beat variability of fetal myocardial perfor-

mance index. Ultrasound Obstet Gynecol 2017; 50(2): 215-20. http://dx.doi.org/10.1002/uog.16012 PMID: 27392316

[26] Lee MY, Won HS, Park JE, *et al.* Fetal left modified myocardial performance index measured by the Auto Mod-MPI system: Development of reference values and application to recipients of twin-to-twin transfusion syndrome. Prenat Diagn 2016; 36(5): 424-31. http://dx.doi.org/10.1002/pd.4798 PMID: 26921842

[27] Lee MY, Won HS, Jeon EJ, *et al.* Feasibility of using auto Mod-MPI system, a novel technique for automated measurement of fetal modified myocardial performance index. Ultrasound Obstet Gynecol 2014; 43(6): 640-5. http://dx.doi.org/10.1002/uog.13247 PMID: 24214891

[28] Cruz-Martínez R, Figueras F, Bennasar M, *et al.* Normal reference ranges from 11 to 41 weeks' gestation of fetal left modified myocardial performance index by conventional doppler with the use of stringent criteria for delimitation of the time periods. Fetal Diagn Ther 2012; 32(1-2): 79-86. http://dx.doi.org/10.1159/000330798 PMID: 22759646

[29] Khandoker AH, Al-Angari HM, Marzbanrad F, Kimura Y. Investigating fetal myocardial function in heart anomalies by doppler myocardial performance indices. Conf Proc IEEE Eng Med Biol Soc 2017; 2017: 2197-200. http://dx.doi.org/10.1109/EMBC.2017.8037290 PMID: 29060332

[30] Zanardini C, Fichera A, Calza S, *et al.* Longitudinal reference ranges for serial measurements of myocardial performance index (MPI) by conventional and pulsed-wave tissue doppler in monochorionic diamniotic twins at 17 to 26 weeks of gestation. Prenat Diagn 2018. Epub ahead of print http://dx.doi.org/10.1002/pd.5286 PMID: 29799131

[31] Willruth A, Steinhard J, Enzensberger C, *et al.* Fetal colour tissue doppler imaging (cTDI): Biventricular reference ranges for the time segments of the cardiac cycle in second and third trimesters of gestation. Arch Gynecol Obstet 2016; 294(5): 917-24. http://dx.doi.org/10.1007/s00404-016-4076-z PMID: 27016345

[32] Meriki N, Welsh AW. Development of Australian reference ranges for the left fetal modified myocardial performance index and the influence of caliper location on time interval measurement. Fetal Diagn Ther 2012; 32(1-2): 87-95. http://dx.doi.org/10.1159/000334133 PMID: 22759698

[33] Clur SA, Oude Rengerink K, Mol BW, Ottenkamp J, Bilardo CM. Fetal cardiac function between 11 and 35 weeks' gestation and nuchal translucency thickness. Ultrasound Obstet Gynecol 2011; 37(1): 48-56. http://dx.doi.org/10.1002/uog.8807 PMID: 20737458

[34] Comas M, Crispi F, Gómez O, Puerto B, Figueras F, Gratacós E. Gestational age- and estimated fetal weight-adjusted reference ranges for myocardial tissue doppler indices at 24-41 weeks' gestation. Ultrasound Obstet Gynecol 2011; 37(1): 57-64. http://dx.doi.org/10.1002/uog.8870 PMID: 21046540

[35] Rozmus-Warcholinska W, Wloch A, Acharya G, *et al.* Reference values for variables of fetal cardiocirculatory dynamics at 11-14 weeks of gestation. Ultrasound Obstet Gynecol 2010; 35(5): 540-7. http://dx.doi.org/10.1002/uog.7595 PMID: 20178107

[36] Van Mieghem T, Gucciardo L, Lewi P, *et al.* Validation of the fetal myocardial performance index in the second and third trimesters of gestation. Ultrasound Obstet Gynecol 2009; 33(1): 58-63. http://dx.doi.org/10.1002/uog.6238 PMID: 18973212

[37] Hernandez-Andrade E, Figueroa-Diesel H, Kottman C, *et al.* Gestational-age-adjusted reference values for the modified myocardial performance index for evaluation of fetal left cardiac function. Ultrasound Obstet Gynecol 2007; 29(3): 321-5. http://dx.doi.org/10.1002/uog.3947 PMID: 17290412

[38] Chen Q, Sun XF, Liu HJ. Assessment of myocardial performance in fetuses by using Tei index. Z Red Flower F UC Hank EZ AZ Hi 2006; 41(6): 387-90. PMID: 16831360

[39] Eidem BW, Edwards JM, Cetta F. Quantitative assessment of fetal ventricular function: Establishing normal values of the myocardial performance index in the fetus. Echocardiography 2001; 18(1): 9-13. http://dx.doi.org/10.1046/j.1540-8175.2001.t01-1-00009.x PMID: 11182775

[40] Tsutsumi T, Ishii M, Eto G, Hota M, Kato H. Serial evaluation for myocardial performance in fetuses and neonates using a new doppler index. Pediatr Int 1999; 41(6): 722-7. http://dx.doi.org/10.1046/j.1442-200x.1999.01155.x PMID: 10618901

[41] Zaharie GC, Hasmasanu M, Blaga L, Matyas M, Muresan D, Bolboaca SD. Cardiac left heart morphology and function in newborns with intrauterine growth restriction: Relevance for long-term assessment. Med Ultrason 2019; 21(1): 62-8. http://dx.doi.org/10.11152/mu-1667 PMID: 30779833

[42] Pacheco Silva C, Araujo Júnior E, Maccagnano Zamith M, *et al.* Assessment of modified myocardial performance index in foetuses with growth restriction. Med Ultrason 2016; 18(2): 207-13. http://dx.doi.org/10.11152/mu.2013.2066.182.idx PMID: 27239656

[43] Chawengsettakul S, Russameecharoen K, Wanitpongpan P. Fetal cardiac function measured by myocardial performance index of small-for-gestational age fetuses. J Obstet Gynaecol Res 2015; 41(2): 222-8. http://dx.doi.org/10.1111/jog.12508 PMID: 25158601

[44] Sharma B, Verma A, Meena C, Gurjar A, Chakraborty A, Srivastav A. Assessment of the cardiac function in intrauterine growth-restricted fetuses and appropriate for gestational age fetuses. J Obstet Gynaecol India 2019; 69(4): 313-6. http://dx.doi.org/10.1007/s13224-018-1192-7 PMID: 31391736

[45] Nassr AA, Youssef AA, Zakherah MS, Ismail AM, Brost BC. Clinical application of fetal left modified myocardial performance index in the evaluation of fetal growth restriction. J Perinat Med 2015; 43(6): 749-54. http://dx.doi.org/10.1515/jpm-2014-0018 PMID: 24706424

[46] Altın H, Karaarslan S, Karataş Z, Alp H, Şap F, Baysal T. Evaluation of cardiac functions in term small for gestational age newborns with mild growth retardation: A serial conventional and tissue doppler imaging echocardiographic study. Early Hum Dev 2012; 88(9): 757-64. http://dx.doi.org/10.1016/j.earlhumdev.2012.04.003 PMID: 22591553

[47] Bhorat IE, Bagratee JS, Pillay M, Reddy T. Determination of the myocardial performance index in deteriorating grades of intrauterine growth restriction and its link to adverse outcomes. Prenat Diagn 2015; 35(3): 266-73. http://dx.doi.org/10.1002/pd.4537 PMID: 25394754

[48] Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Changes in myocardial performance index and aortic isthmus and ductus venosus doppler in term, small-for-gestational age fetuses with normal umbilical artery pulsatility index. Ultrasound Obstet Gynecol 2011; 38(4): 400-5. http://dx.doi.org/10.1002/uog.8976

[49] Comas M, Crispi F, Cruz-Martinez R, Figueras F, Gratacos E. Tissue Doppler echocardiographic markers of cardiac dysfunction in small-for-gestational age fetuses. Am J Obstet Gynecol 2011; 205(1): 57.e1-6. http://dx.doi.org/10.1016/j.ajog.2011.03.010 PMID: 21620362

[50] Benavides-Serralde A, Scheier M, Cruz-Martinez R, *et al.* Changes in central and peripheral circulation in intrauterine growth-restricted fetuses at different stages of umbilical artery flow deterioration: New fetal cardiac and brain parameters. Gynecol Obstet Invest 2011; 71(4): 274-80. http://dx.doi.org/10.1159/000323548 PMID: 21346314

[51] Bhorat I, Pillay M, Reddy T. The clinical prognostic significance of myocardial performance index (MPI) in stable placental-mediated disease. Cardiovasc J Afr 2018; 29(5): 310-6. http://dx.doi.org/10.5830/CVJA-2018-036

[52] Niewiadomska-Jarosik K, Zamojska J, Zamecznik A, Wosiak A, Jarosik P, Stańczyk J. Myocardial dysfunction in children with intrauterine growth restriction: An echocardiographic study. Cardiovasc J Afr 2017; 28(1): 36-9. http://dx.doi.org/10.5830/CVJA-2016-053

[53] Crispi F, Hernandez-Andrade E, Pelsers MMAL, *et al.* Cardiac dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. Am J Obstet Gynecol 2008; 199(3):

254.e1-8.
http://dx.doi.org/10.1016/j.ajog.2008.06.056 PMID: 18771973

[54] Henry A, Alphonse J, Tynan D, Welsh AW. Fetal myocardial performance index in assessment and management of small-for-gestational-age fetus: a cohort and nested case-control study. Ultrasound Obstet Gynecol 2018; 51(2): 225-35.
http://dx.doi.org/10.1002/uog.17476 PMID: 28345186

[55] Ichizuka K, Matsuoka R, Hasegawa J, *et al.* The Tei index for evaluation of fetal myocardial performance in sick fetuses. Early Hum Dev 2005; 81(3): 273-9.
http://dx.doi.org/10.1016/j.earlhumdev.2004.07.003 PMID: 15814209

[56] Eixarch E, Hernandez-Andrade E, Crispi F, *et al.* Impact on fetal mortality and cardiovascular Doppler of selective ligature of uteroplacental vessels compared with undernutrition in a rabbit model of intrauterine growth restriction. Placenta 2011; 32(4): 304-9.
http://dx.doi.org/10.1016/j.placenta.2011.01.014 PMID: 21334065

[57] Cruz-Martinez R, Figueras F, Benavides-Serralde A, Crispi F, Hernandez-Andrade E, Gratacos E. Sequence of changes in myocardial performance index in relation to aortic isthmus and ductus venosus doppler in fetuses with early-onset intrauterine growth restriction. Ultrasound Obstet Gynecol 2011; 38(2): 179-84.
http://dx.doi.org/10.1002/uog.8903 PMID: 21154784

[58] Henry A, Gopikrishna S, Mahajan A, Alphonse J, Meriki N, Welsh AW. Use of the foetal myocardial performance index in monochorionic, diamniotic twin pregnancy: A prospective cohort and nested case-control study. J Matern Fetal Neonatal Med 2019; 32(12): 2017-29.
http://dx.doi.org/10.1080/14767058.2018.1424817 PMID: 29301441

[59] Bhorat IE, Bagratee JS, Reddy T. Assessment of fetal myocardial performance in severe early onset pre-eclampsia (EO-PET) with and without intrauterine growth restriction across deteriorating stages of placental vascular resistance and links to adverse outcomes. Eur J Obstet Gynecol Reprod Biol 2017; 210: 325-33.
http://dx.doi.org/10.1016/j.ejogrb.2017.01.014 PMID: 28113071

[60] Hernandez-Andrade E, Crispi F, Benavides-Serralde JA, *et al.* Contribution of the myocardial performance index and aortic isthmus blood flow index to predicting mortality in preterm growth-restricted fetuses. Ultrasound Obstet Gynecol 2009; 34(4): 430-6.
http://dx.doi.org/10.1002/uog.7347 PMID: 19790100

[61] Ortiz JU, Torres X, Eixarch E, *et al.* Differential changes in myocardial performance index and its time intervals in donors and recipients of twin-to-twin transfusion syndrome before and after laser therapy. Fetal Diagn Ther 2018; 44(4): 305-10.
http://dx.doi.org/10.1159/000485380 PMID: 29353282

[62] Gijtenbeek M, Eschbach SJ, Middeldorp JM, *et al.* The value of echocardiography and Doppler in the prediction of fetal demise after laser coagulation for TTTS: A systematic review and meta-analysis. Prenat Diagn 2019; 39(10): 838-47.
http://dx.doi.org/10.1002/pd.5511 PMID: 31237967

[63] Leszczyńska K, Preis K, Swiatkowska-Freund M, Pankrac Z. Comparison of fetal myocardial contractility before and after laser photocoagulation of communicating vessels in twin-to-twin transfusion syndrome. Ginekol Pol 2014; 85(4): 283-6.
http://dx.doi.org/10.17772/gp/1724 PMID: 24834706

[64] Delabaere A, Leduc F, Reboul Q, *et al.* Prediction of neonatal outcome of TTTS by fetal heart and doppler ultrasound parameters before and after laser treatment. Prenat Diagn 2016; 36(13): 1199-205.
http://dx.doi.org/10.1002/pd.4956 PMID: 27813120

[65] Finneran MM, Pickens R, Templin M, Stephenson CD. Impact of recipient twin preoperative myocardial performance index in twin-twin transfusion syndrome treated with laser. J Matern Fetal Neonatal Med 2017; 30(7): 767-71.
http://dx.doi.org/10.1080/14767058.2016.1187124 PMID: 27150066

[66] Zanardini C, Prefumo F, Fichera A, Botteri E, Frusca T. Fetal cardiac parameters for prediction of twin-to-twin transfusion syndrome. Ultrasound Obstet Gynecol 2014; 44(4): 434-40.
http://dx.doi.org/10.1002/uog.13442 PMID: 24919586

[67] Papanna R, Mann LK, Molina S, Johnson A, Moise KJ. Changes in the recipient fetal Tei index in the peri-operative period after laser photocoagulation of placental anastomoses for twin-twin transfusion syndrome. Prenat Diagn 2011; 31(2): 176-80.
http://dx.doi.org/10.1002/pd.2673 PMID: 21268037

[68] Bhorat I, Pillay M, Reddy T. Determination of the fetal myocardial performance index in women with gestational impaired glucose tolerance and to assess whether this parameter is a possible prognostic indicator of adverse fetal outcome. J Matern Fetal Neonatal Med 2018; 31(15): 2019-26.
http://dx.doi.org/10.1080/14767058.2017.1334047 PMID: 28532199

[69] Mohsin M, Sadqani S, Younus K, Hoodbhoy Z, Ashiqali S, Atiq M. Evaluation of cardiac function in fetuses of mothers with gestational diabetes. Cardiol Young 2019; 29(10): 1264-7.
http://dx.doi.org/10.1017/S1047951119001884 PMID: 31475665

[70] Bhorat I, Pillay M, Reddy T. Assessment of the fetal myocardial performance index in well-controlled gestational diabetics and to determine whether it is predictive of adverse perinatal outcome. Pediatr Cardiol 2019; 40(7): 1460-7.
http://dx.doi.org/10.1007/s00246-019-02158-4 PMID: 31324952

[71] Figueroa H, Silva MC, Kottmann C, *et al.* Fetal evaluation of the modified-myocardial performance index in pregnancies complicated by diabetes. Prenat Diagn 2012; 32(10): 943-8.
http://dx.doi.org/10.1002/pd.3937 PMID: 22825924

[72] Pilania R, Sikka P, Rohit MK, Suri V, Kumar P. Fetal Cardiodynamics by echocardiography in insulin dependent maternal diabetes and its correlation with pregnancy outcome. J Clin Diagn Res 2016; 10(7): QC01-4.
http://dx.doi.org/10.7860/JCDR/2016/17993.8079 PMID: 27630907

[73] Russell NE, Foley M, Kinsley BT, Firth RG, Coffey M, McAuliffe FM. Effect of pregestational diabetes mellitus on fetal cardiac function and structure. Am J Obstet Gynecol 2008; 199(3): 312.e1-7.
http://dx.doi.org/10.1016/j.ajog.2008.07.016 PMID: 18771996

[74] Sanhal CY, Daglar HK, Kara O, Uygur D, Yucel A. Assessment of fetal myocardial performance index in women with pregestational and gestational diabetes mellitus. J Obstet Gynaecol Res 2017; 43(1): 65-72.
http://dx.doi.org/10.1111/jog.13174 PMID: 27862741

[75] Turan S, Turan OM, Miller J, Harman C, Reece EA, Baschat AA. Decreased fetal cardiac performance in the first trimester correlates with hyperglycemia in pregestational maternal diabetes. Ultrasound Obstet Gynecol 2011; 38(3): 325-31.
http://dx.doi.org/10.1002/uog.9035 PMID: 21538641

[76] Patey O, Carvalho JS, Thilaganathan B. Perinatal changes in fetal cardiac geometry and function in diabetic pregnancy at term. Ultrasound Obstet Gynecol 2019; 54(5): 634-42.
http://dx.doi.org/10.1002/uog.20187 PMID: 30520203

[77] Bhorat IE, Bagratee JS, Pillay M, Reddy T. Use of the myocardial performance index as a prognostic indicator of adverse fetal outcome in poorly controlled gestational diabetic pregnancies. Prenat Diagn 2014; 34(13): 1301-6.
http://dx.doi.org/10.1002/pd.4471 PMID: 25088046

[78] Wong ML, Wong WH, Cheung YF. Fetal myocardial performance in pregnancies complicated by gestational impaired glucose tolerance. Ultrasound Obstet Gynecol 2007; 29(4): 395-400.
http://dx.doi.org/10.1002/uog.3957 PMID: 17330321

[79] Bui YK, Kipps AK, Brook MM, Moon-Grady AJ. Tissue Doppler is more sensitive and reproducible than spectral pulsed-wave Doppler for fetal right ventricle myocardial performance index determination in normal and diabetic pregnancies. J Am Soc Echocardiogr 2013; 26(5): 507-14.
http://dx.doi.org/10.1016/j.echo.2013.02.006 PMID: 23498900

[80] Balli S, Kibar AE, Ece I, Oflaz MB, Yilmaz O. Assessment of fetal cardiac function in mild preeclampsia. Pediatr Cardiol 2013; 34(7): 1674-9.
http://dx.doi.org/10.1007/s00246-013-0702-8 PMID: 23591803

[81] Crispi F, Comas M, Hernández-Andrade E, *et al.* Does pre-eclampsia influence fetal cardiovascular function in early-onset intrauterine growth restriction? Ultrasound Obstet Gynecol 2009; 34(6): 660-5.
http://dx.doi.org/10.1002/uog.7450 PMID: 19827117

[82] Api O, Emeksiz MB, Api M, Ugurel V, Unal O. Modified myocar-

dial performance index for evaluation of fetal cardiac function in pre-eclampsia. Ultrasound Obstet Gynecol 2009; 33(1): 51-7. http://dx.doi.org/10.1002/uog.6272 PMID: 19086000

[83] Youssef L, Miranda J, Paules C, *et al.* Fetal cardiac remodeling and dysfunction is associated with both preeclampsia and fetal growth restriction. Am J Obstet Gynecol 2020; 222(1): 79.e1-9. http://dx.doi.org/10.1016/j.ajog.2019.07.025 PMID: 31336074

[84] Ozel A, Alici Davutoglu E, Eric Ozdemir M, Oztunc F, Madazli R. Assessment of fetal left ventricular modified myocardial performance index and its prognostic significance for adverse perinatal outcome in intrahepatic cholestasis of pregnancy. J Matern Fetal Neonatal Med 2018; 33(12): 2000-5. http://dx.doi.org/10.1080/14767058.2018.1535588 PMID: 30309274

[85] Henry A, Welsh AW. Monitoring intrahepatic cholestasis of pregnancy using the fetal myocardial performance index: a cohort study. Ultrasound Obstet Gynecol 2015; 46(5): 571-8. http://dx.doi.org/10.1002/uog.14769 PMID: 25516144

[86] Sanhal CY, Kara O, Yucel A. Can fetal left ventricular modified myocardial performance index predict adverse perinatal outcomes in intrahepatic cholestasis of pregnancy? J Matern Fetal Neonatal Med 2017; 30(8): 911-6. http://dx.doi.org/10.1080/14767058.2016.1190824 PMID: 27186866

[87] Cruz-Lemini M, Crispi F, Van Mieghem T, *et al.* Risk of perinatal death in early-onset intrauterine growth restriction according to gestational age and cardiovascular doppler indices: A multicenter study. Fetal Diagn Ther 2012; 32(1-2): 116-22. http://dx.doi.org/10.1159/000333001 PMID: 22777088

[88] Gapp-Born E, Sananes N, Guerra F, *et al.* Predictive value of cardiovascular parameters in stages 1 and 2 of twin-to-twin transfusion syndrome. Prenat Diagn 2014; 34(9): 908-14. http://dx.doi.org/10.1002/pd.4393 PMID: 24760447

[89] Stirnemann JJ, Mougeot M, Proulx F, *et al.* Profiling fetal cardiac function in twin-twin transfusion syndrome. Ultrasound Obstet Gynecol 2010; 35(1): 19-27. http://dx.doi.org/10.1002/uog.7488 PMID: 20020467

[90] Delabaere A, Leduc F, Reboul Q, *et al.* Factors associated to early intrauterine fetal demise after laser for TTTS by preoperative fetal heart and doppler ultrasound. Prenat Diagn 2018; 38(7): 523-30. http://dx.doi.org/10.1002/pd.5280 PMID: 29740835

[91] Eixarch E, Valsky D, Deprest J, *et al.* Preoperative prediction of the individualized risk of early fetal death after laser therapy in twin-to-twin transfusion syndrome. Prenat Diagn 2013; 33(11): 1033-8. http://dx.doi.org/10.1002/pd.4191 PMID: 23813911

[92] Iwagaki S, Takahashi Y, Chiaki R, Asai K, Matsui M, Katsura D. Case of resuscitation from cardiac failure by intrauterine transfusion after single fetal death in monochorionic twin pregnancy. J Obstet Gynaecol Res 2019; 45(10): 2105-10. http://dx.doi.org/10.1111/jog.14082 PMID: 31368163

[93] Aggarwal S, Natarajan G. Echocardiographic correlates of persistent pulmonary hypertension of the newborn. Early Hum Dev 2015; 91(4): 285-9. http://dx.doi.org/10.1016/j.earlhumdev.2015.02.008 PMID: 25782054