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Fetal cardiac function: myocardial performance index

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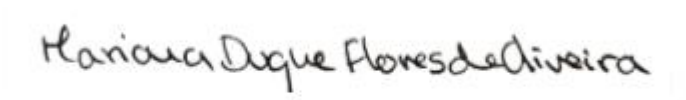

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Resumo

O Índice de Perfomance Miocárdica (IMP) apresentado por Tei em 1995 é o rácio entre a soma do tempo de contração isovolumétrica (TCI) com o tempo de relaxamento isovolumétrico (TRI) e o tempo de ejeção (TE). O IMP Modificado, proposto em 2005 é considerado uma ferramenta útil e fiável no estudo da função cardíaca fetal em diversas condições como restrição de crescimento, síndrome de transfusão feto-fetal, diabetes materna, pré-eclâmpsia, colestase intra-hepática da gravidez e desfecho perinatal desfavorável.

Todavia, a aplicabilidade clínica é limitada pela pobreza na standardização da metodologia como sejam variações na técnica, definições do ecógrafo, posicionamento do *calliper* e experiência necessária, que pode resultar em valores de IMP significativamente diferentes.

Esta revisão fornece uma pesquisa na literatura relevante acerca do IMP, apresenta metodologia rigorosa e consideraçoes técnicas assim como propõe investigação futura.

Índice

Title: Fetal cardiac function: myocardial performance index.

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Abbreviations

AI, Angle of Insonation
AGA, Appropriate-for-Gestational Age
DSV, Doppler Sweep Velocity
DG, Doppler Gain
ET, Ejection Time
ECMO, Extra-Corporeal Membrane Oxygenation
FD, Fetal Death
GA, Gestational Age
GDM, Gestational Diabetes Mellitus
GIGT, Gestational Impaired Glucose Tolerance
ICP, Intrahepatic Cholestasis of Pregnancy
ICT, Isovolumetric Contraction Time
IRT, Isovolumetric Relaxation Time
IUGR, Intrauterine Growth Restriction
LV-MPI, Left Ventricle Myocardial Performance Index
LV-MPI', Tissue Doppler Left Ventricle Myocardial Performance Index
MCTP, Monochorionic Twin Pregnancy
Mod-MPI, Modified Myocardial Performance Index
MPI, Myocardial Performance Index
PDP, Pregestational Diabetic pregnancies
PPHN, Persistent Pulmonary Hypertension of the Newborn
PE, Preeclampsia
RV-MPI, Right Ventricle Myocardial Performance Index
RV-MPI', Tissue Doppler Right Ventricle Myocardial Performance Index
SBA, Serum Bile Acids
SGA, Small-for-Gestational Age
sIUGR, selective IUGR
SLPCV, Selective Laser Photocoagulation of Communicating Vessels
SV, Sample Volume
TDI, Tissue Doppler Imaging
TTTS, Twin-twin transfusion syndrome
UA, Umbilical Artery
WMF, Wall Motion Filter

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 outcome.

Nevertheless, clinical translation is currently limited by poorly standardised methodology as variations in technique, machine settings, calliper placement and specific training required that can result in significantly different MPI values.

This review serves to provide a survey of the relevant literature on MPI, to present a strict methodology and technical considerations and to propose future research.

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

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 the 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], is accessible and can be used in pregnancy to determine[9] normal physiologic and underlying pathophysiologic characteristics.[10,11]

As a result of advances in this technology there is a better visualization of the fetal heart early, in the first trimester,[11] important achievement for fetal intervention, time of delivery[12] and other management decisions. Early diagnosis of cardiac defects allows families to prepare for the birth of a sick child. Distinctly, this helps on reducing the anxiety of high risk patients who have previous family history of cardiac defects.[4,13]

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 easily be 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).[4,5,14,15,16] 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 until 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 potential useful predictor of global cardiac function, which is not influenced by heart size, shape, orientation, geometry or rate. [3,17,18] Its application in fetus has advantages over the application in adults since it is possible to measure the atrioventricular and semilunar valves flows simultaneously, removing the inaccuracy predisposed in measuring in different heart beats. [4]

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, pre-

eclampsia, 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 [3]as variations in technique, machine settings, calliper placement and specific training required that 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 showed 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 future research.

Methods

To compose this review, thorough literature searches were repeatedly conducted in PubMed and Medline with a limitation of articles written in the English language. The search terms used were fetal heart, doppler, fetal echocardiography, fetal myocardial performance index, heart function. Additionally, the references of all analysed studies were searched to obtain necessary information.

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]

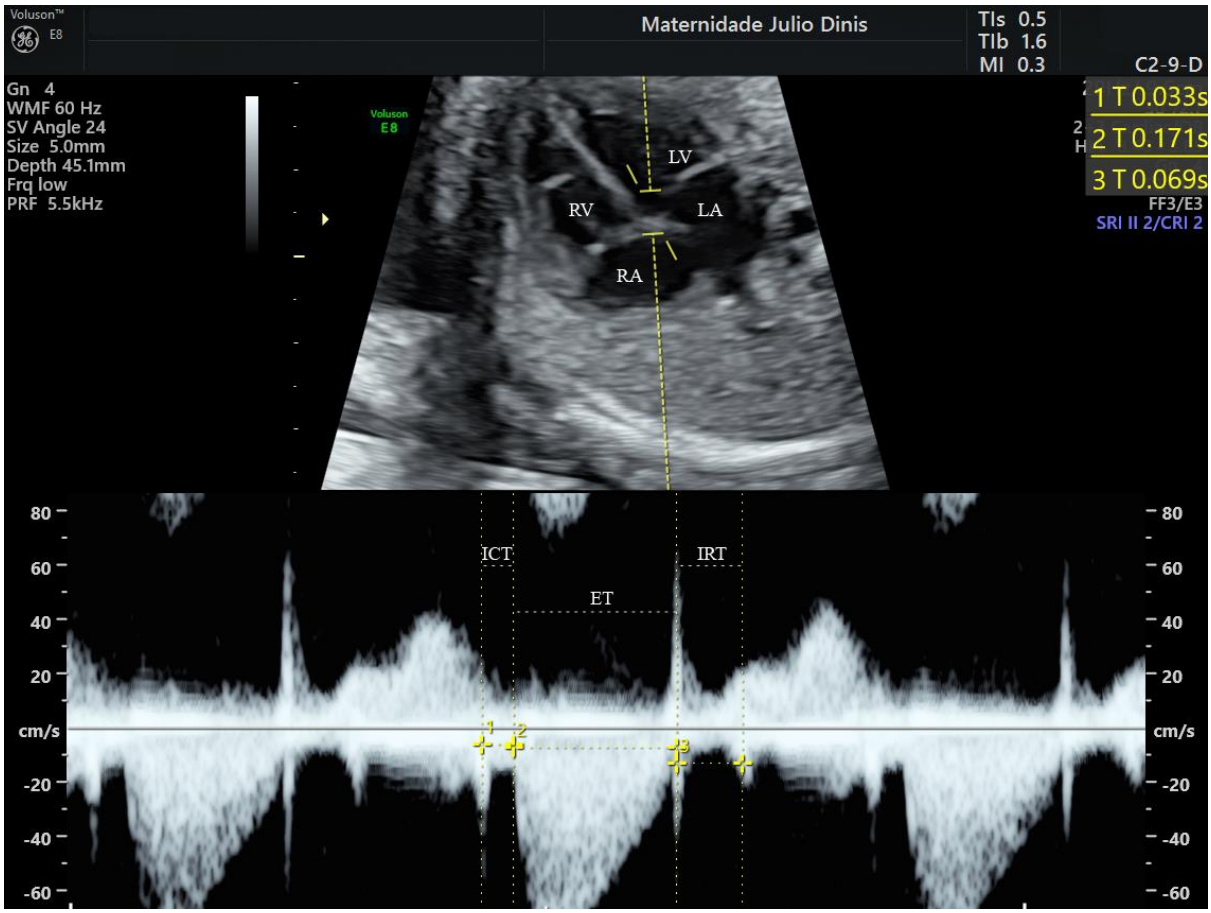

Figure 3. Mod-MPI Doppler waveform, showing the time intervals (ICT, IRT and ET).

The ideal images should be obtained in the absence of fetal movements and with the suspension of maternal respiration, which may difficult the sample volume placement.[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 maximum 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 in 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 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 Roboissom et al.[3] Later, Hernandez et al. developed the using of the mitral valve closing click also and clearly defining the three time intervals by visualizing the clicks of both valves (Mod-MPI)[3,12]

Several studies used the method for the Mod-MPI measurement recommend by Hernandez-Andrade et al 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.[2,6,12,16,18,21,23,25,26,27,28]

Values can be affected by ultrasound machine settings as calliper 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, it is recommended the use of the same ultrasound equipment during patient follow-up and specific reference ranges for each ultrasound system.[2,23]

About calliper placement, the opening and closing of valve leaflets produces "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 can be achieved with thinner clicks. The calliper can be placed at the beggining, from the end to the beginning of the valve clicks (corresponding to physiological time intervals), at the peak or end of the valve clicks.[2,15,24]

Hernandez et al. described as optimal settings the SV of 3mm, the AI <30°, the fastest possible DSV to create greater horizontal stretch and valve clicks visualization (15cm/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 clearly 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 with a fixed WMF at 300Hz, defined that the angle of insonation should be kept less than 15°, Doppler aliasing avoided and the measurement should be at the peak of valve clicks. [24]

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

Some other studies 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 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 were developed and can remove this 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 which previously requires the operator to manually select a region of interest in the Doppler waveform before any upcoming image analysis can occur.[24,27]

Maheshwari P, Henry A and Welsh AW have developed a novel automated MPI system that automatically locates valve click peaks and calculates the Mod-MPI. [24]

Tissue Doppler imaging (TDI) was also proposed to measure MPI. Both spectral or 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 wich 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 TDI method may be more sensitive, has less variability and more precision than conventional MPI.[6,10]

Reference ranges of myocardial performance index

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] RV MPI [0.304;0.557] LV MPI' [0.350;0.643] RV MPI' [0.398;0.632]	Increasing trend with the GA.
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;054]	
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		[0.32 ± 0.16]		0.31 ± 0.12]		
			35	28–32 weeks		[0.35 ± 0.22]		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]					
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]				Constant throughout gestation.	
					RV MPI [0.332 ± 0.079]					
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	Prospective cross-sectional study	117	20–36 weeks	LV MPI [0.34 ± 0.05]				Independent of GA.	

	population and in a population at risk for cardiac failure because of volume overload (recipient fetuses in cases of twin–twin transfusion syndrome (TTTS)).					
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 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]	Decreasing trend with the GA.
					RV MPI [0.39 ± 0.04]	
				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 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 difficulty on the clinical application of MPI was based on the absence of standardized measurement, on the unclearness of the relationship with advancing gestational age (GA) and the variations in normal reference values (Table 1). The 20 studies in the table tried to define reference ranges including LV MPI, RV MPI, LV Mod-MPI, LV MPI' or RV MPI' values depending on each article. GA varied from 11 to 40 weeks.

The minimum and maximum values reported for LV MPI are 0.16[33] and 0,69[40] and for the 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 didn't specify a MPI variation trend.[19,33] Two MPI studies[35,39] and two MPI' studies[31,34] showed that the values remain constant with advancing GA. Another three MPI studies found that MPI is independent of GA.[3,22,36] There was a study that indicated that Mod-MPI remains constant from 20 to 26 weeks and decreases with advancing GA.[18] A decrease of MPI with advancing GA was found in two other studies[38,40].

The most frequent variation trend was the increase of the values with advancing GA. One study reported an increase of MPI with advancing GA[30] and there were seven studies which noticed an increase of Mod-MPI with advancing GA. [6,23,12,26,28,32,37] 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 better inter-observer correlation in late pregnancy, suggesting that measurements may be more reliable and reproducible later in pregnancy.[12]

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.[41,42,43]

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, 44,45,46]

Some authors have described subsequent alterations in the cardiac geometry and shape, such as a spherical shape resultant of ventricular dilation rather than an increasing myocardial hypertrophy.[41]

This situation leads to systolic and/or diastolic dysfunction presented 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, a relative increase of 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 named cardiac remodeling.[44]

It was presented a higher MPI 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. [48,49,50]

An elevated MPI has been reported in IUGR fetuses[40,44,47,51,52,53]and newborns.[41,46] A few studies did not find a significant difference between both 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 demonstrated 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]

Respecting 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 pre-eclampsia and IUGR pregnancies, there is a fetal cardiac function aggravation and MPI tracking could enable a better monitorization.[59]

Abnormal MPI in IUGR was also associated with adverse perinatal outcome, increased morbidity and death. [45,47,53,60]

Thus, MPI is important as an evaluation tool for suspected IUGR, preventing adverse short and long-term outcomes. [47]

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 early stages of the disease.[57,62,63,64,65,66]

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.[61,57] The fetus adaptive capacities and the myocardial status before surgery influence the cardiac response.[63]

On 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 recipients and shorten of 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 by 12-24 hours. The right-sided Tei index reduced even more 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.

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. [68,69,70,71]

In PDP fetuses, MPI can evince early cardiac function alterations preceding the structural changes. [72,73] In fact, a higher fetal MPI [69,70,71,73,74,75] 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], when compared with 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 for insulin to 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 the 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 in gestational impaired glucose tolerance (GIGT), as well as in these fetuses with and 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]

Assessment of myocardial performance index and preeclampsia

As IUGR, 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 doesn't have an impact on 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 reflects both systolic and diastolic dysfunction in fetuses with growth restriction.[83] Another study showed a higher median Mod-MPI (due to all its components) in 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 outcome. 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 outcome.[59]

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, beingan identified cause of sudden intrauterine fetal death.[84,85]

The presence of elevated maternal serum bile acids (SBA) levels may have effects on 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.[84,85,86] Two of them registered the 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 outcome was found. A study suggested the cut-off of MPI >0.48.[84,86]

Assessment of myocardial performance index and adverse perinatal outcome

In most of the cases, there is an association between elevation of MPI and increase of adverse perinatal outcome. It appeared 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 were the outcomes. MPI was considered a significant predictor of adverse outcome.[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 were proposed. Adverse outcomes were defined by perinatal death, neonatal resuscitation, hypoxic ischaemic 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 were 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 outcome, the majority of co-twins of a single FD in a MCTP with superficial anastomoses had poor outcomes. The recipients' MPI decreased promptly after this procedure and cardiac function was 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 outcome.[70,77] A cut-off value >= 0,52 was proposed.[77] The main adverse outcomes were low Apgars, hypoglycaemia, polycythemia, low pH, perinatal death, admission to the neonatal intensive care unit, cord pH <7.15 and presence of cardiomyopathy.[70,77] MPI was presented as an excellent predictor of adverse outcome in GIGT group, showing elevated MPI when compared to fetuses with normal outcome.[68]

About ICP, there's an association between high SBA and cholestatics 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 with a PPHN group, the LVMPI tended to be higher in cases of adverse outcomes [death or that required ECMO (extra-corporeal membrane oxygenation)]. The causes of death were hypoxemic respiratory failure, inborn error of metabolism, trisomy, acute renal failure, disseminated herpes simplex viral infection, sepsis, cerebral infarct, intracerebral bleed and hypoxic-ischemic encephalopathy.[93]

Discussion

MPI may have a great value as a noninvasive marker of global myocardial function and may be 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 methodology such as variations in 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), Doppler aliasing avoided 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. [6,23,12,26,28,30,32,37]

The evaluation of SGA fetuses showed an elevated MPI.[43,48] Although UA flow is the clinical standard to differentiate SGA and IUGR, alterations in cardiac function parameters as MPI were found in fetuses with normal UA Doppler, expressing late-onset forms of IUGR. [48,49,50] IUGR fetuses showed an elevated MPI in most of the studies[40,44,47,51,52,53] and this index increases throughout the deterioration stages. [47,53]

Regarding TTTS, MPI appeared to be significantly elevated in future recipients and lower in donors, before diagnosis.[66] It also appeared to predict which cases would advance to TTTS in cases where

there is only liquor and/or growth discordance at presentation.[57] An abnormal Mod-MPI in recipient twins was referred in an automated analysis.[26] A higher MPI in both donors and recipients was presented, at all severity stages, when compared to uncomplicated monochorionic twins, although MPI in recipients was higher than in donors.[61] After the treatment (SLPCV), MPI and MPI' demonstrated an improvement.[30,61,63,65] About the pre-, intra- and post- operative periods, a study showed that MPI worsens during the intra-operative period, before returning to pre-operative levels by 12-24 hours[67]. A different study found that an increase in pre-operative recipient RVMPI was associated with decreased survival at 30 days.[64]

MPI can evince early cardiac function alterations in diabetes' cases, [72,73] MPI and MPI' showed an increase in PDP and GDM[69,70,71,73,74,75,76] and two studies found that this increase is independent of the onset of DM. [71,74] The requirement for insulin to glycemic control presented higher Mod-MPI than the requirement of diet alone.[71] It was also increased in both poorly and well-controlled diabetics, in comparison with healthy pregnancies. [70,72,73,75,77]

Pertaining to PE, three studies found an elevated MPI in pregnancies complicated by this condition while other two suggested that PE per se doesn't influence MPI. [51,59,80,81,82]

Regarding ICP, MPI values were increased in these cases. [84,85,86] Increasing maternal SBA levels were related to an increase in LVMPI in one study, although a different study did not find any correlation.[84,85]

There was no significant difference between MPI values in mild and severe ICP cases.[84,85]

In cases of IUGR, TTTS, maternal diabetes, persistent pulmonary hypertension of the newborn (PPHN) and indirectly, in ICP, MPI was considered an adverse outcome predictor. [47,60,70,77,85,88,93]

As shown above, MPI elevations were evidenced in different pathologic status that affect the fetal systolic and diastolic cardiac function. These results reinforce its clinical relevance once a demarcation of reference values of normality is achieved. It would be of great importance in the diagnose of these pathologies and in real time evaluation of high-risk pregnancies during maturation and development of the fetus.

Ethics Committee Approval

N/A

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Author Contributions

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Conflicts of Interest

We have no conflicts of interest in this review.

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