Development of Normal Gestational Ranges for the Right Myocardial Performance Index in the Australian Population with Three Alternative Caliper Placements

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Key Words

Modified myocardial performance index · Fetal cardiac function · Reference range

Abstract

Objectives: To construct gestational age-adjusted reference ranges for the right fetal modified myocardial performance index (RMPI) in an Australian population and to assess the influence of valve click caliper position on constituent time intervals and the RMPI. **Methods:** A prospective cross-sectional study of RMPI from 235 normal fetuses at 17–38 weeks of gestation was performed. Two Doppler waveforms were obtained: tricuspid and pulmonary valves for 'a' and 'b' readings, respectively. The ultrasound machine settings were: Doppler sweep velocity 15 cm/s, angle of insonation <15°, minimal gain, and wall motion filter 300 Hz. The 'a' and 'b' intervals were measured at three different caliper positions in each fetus: at the beginning of the original valve clicks ('original'), at the beginning of the reflected tricuspid and pulmonary closure clicks ('reflected') and at the peak of valve clicks ('peak'). RMPI was calculated as (a – b)/b. The three readings were obtained and averaged per examination, with intraobserver repeatability assessed by intraclass correlation

coefficient (ICC) and 95% CI. **Results:** For 'original', 'reflected' and 'peak' RMPI, mean ± SD, ICC (95% CI) were: 0.53 ± 0.10, 0.86 (0.83–0.89); 0.48 ± 0.10, 0.84 (0.81–0.87) and 0.48 ± 0.10, 0.89 (0.87–0.91), respectively. The RMPI increased by approximately 15% as gestation increased and decreased slightly with increasing heart rate. **Conclusion:** This is the first publication of reference ranges for RMPI based on caliper position. All methods showed good ICC, including the 'peak' method which we have previously proposed for routine use based on its repeatability and ease of identification when measuring the myocardial performance index.

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Introduction

Accurate repeatable ultrasound measures of fetal cardiac function are an important goal of fetal medicine research, as they might provide information about fetal cardiovascular responses to pathological situations. Translation of such measures from research to clinical practice has been slow, in part because differences between fetal and postnatal life have not been adequately accounted for, and in part due to a lack of stringent validation of techniques [1].

Table 1. Previously published right RMPI reference ranges in normal singleton pregnancies

First author, year	Fetuses, n	GA, weeks	RMPI (mean)	Available comments		Remarks
				relation of RMPI with GA	effect of HR on RMPI	
Tsutsumi [20], 1999	50	18–26 27–33 34–40	0.62 0.53 0.49	RMPI gradually decreased throughout gestation	no effect	plotted graphically
Hamela-Olkowska [30], 2011	140	18–40	0.48	no effect	no effect	in Polish
Clur [31], 2011	31 50 32	11–13 ⁺⁶ 14–21 ⁺⁶ 22–35	0.37 0.3 0.4	no comment	no comment	only mean values given for the normal group; normal group used as comparison group for trisomy 21 fetuses
Clur [32], 2011	120 98 35	11–15 18–22 28–32	0.35 0.32 0.35	MPI remained constant during gestation	no comment	only mean values given for the normal group; fetuses with increased NT were included in their normal range
Ghawi [35], 2013	250	2nd and 3rd trimesters	0.47	independent of GA	independent of HR	plotted graphically
Parasuraman [37], 2013	221	12–40	0.41	little change across gestation	no comment	plotted graphically

GA = Gestational age; NT = nuchal translucency.

Myocardial performance index (MPI) is one such measure of adult cardiac function described by Tei et al. [2], refined for fetal use by Friedman et al. [3] and modified by Hernandez-Andrade et al. [4] using valve clicks to improve accuracy. It measures global ventricular function that is independent of ventricular geometry. Most publications following the introduction of modified MPI (Mod-MPI) focused on the left MPI in both normal and pathological pregnancies [5–10]. The initial focus on left MPI may be due to the ability to acquire it in a single plane [3], thus allowing measurement of concordant isovolumetric time intervals and potentially improving measurement accuracy; however, the translational potential of the left Mod-MPI (LMPI) has been hampered by widely differing reports of the normal range [9, 11–13]. Gestational age-adjusted reference ranges using stringent criteria are now available [14, 15], providing a basis for the exploration of its utility in pathological situations.

Although progressive measurement refinements have improved LMPI calculation [3, 4, 16], the fetus is right heart dominant [17]; therefore, the earliest signs of myocardial dysfunction should be observed in the right side of the heart. It has been reported that the fetal right ventricle is affected to a greater degree than the left by physiological stressors such as increased systemic arterial pressure [18] and that the right ventricle will manifest hypertrophy, dilatation or dysfunction before the left ventricle

in pathological conditions associated with increased preload or afterload [17].

Right Mod-MPI (RMPI) requires the acquisition of two separate waveforms (pulmonary and tricuspid) and has been thought to be less reproducible than LMPI [4]. However, we previously reported similar reproducibility for RMPI and LMPI [19]. Previously published RMPI ranges have widely divergent reported means, from 0.24 to 0.62 in the second and third trimesters of normal singleton fetuses [20–37]. Table 1 highlights previously published RMPI reference ranges in normal singleton pregnancies. Fetal cardiac function using the right MPI has been compared with other cardiovascular modalities [29, 30, 32, 36, 38–41], including tissue versus spectral Doppler [36, 38]. Bui et al. [36] suggest RMPI tissue Doppler to be more sensitive to pathology than spectral RMPI; however, tissue and spectral values correlate well in uncomplicated pregnancies [36, 37]. Use of RMPI has also been studied in pathological pregnancies, including twin-twin transfusion syndrome (TTTS), where RMPI appears to be an early marker of cardiac dysfunction, becoming abnormal prior to either LMPI or other functional echocardiographic markers [41, 42].

Our group has recently published work that aimed to optimize acquisition and measurement of LMPI through further refinement of the machine settings and valve clicks first described by Hernandez-Andrade et al. [4], including production of an Australian gestational age-

based LMPI reference range [11, 14]. In this study, we aimed to apply those techniques to RMPI, evaluate the influence of caliper positions in valve click identification and examine the effect of fetal heart rate on the measurement of RMPI.

Methods

Subjects

This was a prospective cross-sectional study, with all subjects scanned on a single occasion between 17 and 38 completed weeks of gestation (17^{+0} – 37^{+6}). Ethical approval for the study was provided by the local human research ethics committee (SESIAHS HREC 08/168). Women were recruited from the antenatal and ultrasound clinics of a teaching hospital and were eligible for inclusion if they were 18 to 45 years of age, had 17–38 completed weeks of gestation with a singleton pregnancy and had a normal morphology scan. Patients were excluded if they had any known maternal or fetal complication of pregnancy, had a preexisting medical condition for which they were currently taking medication or had insufficient English abilities for valid consent. Data from fetuses subsequently shown to have a serious congenital abnormality were also excluded from the sample. Data were also excluded if on review the images were not considered technically adequate because (1) images with both ‘original’ and ‘reflected’ clicks were not present, (2) the fetal heart rate for the ‘a’ images was >10 beats different from the fetal heart rate for the ‘b’ images and (3) three or more analyzable ‘a’ and ‘b’ time interval images using appropriate machine settings were not obtained. Although there has not been consistent agreement on the level of discrepancy in ‘a’ heart rate (HR) and ‘b’ HR likely to affect interpretation of MPI [32, 35, 36], we felt discrepancies of >10 bpm likely represented a change of fetal state and might bias results. The pregnancy was dated from the woman’s clinically agreed estimated due date, based on last menstrual period date, or by ultrasound dating if this was unreliable or differed substantially from ultrasound dating (≥ 5 days from <12 weeks’ ultrasound, 7 or more days from 12–20 weeks’ ultrasound).

Myocardial Performance Index

All examinations were performed using curvilinear transducers (3.5–7 MHz) of a Voluson 8 Expert (GE Medical Systems, Australia) ultrasound machine, in the absence of fetal movements, by 1 of 3 experience operators (N.M., A.H. and J.S.). Mechanical and thermal indices were maintained below 1.0, the fastest Doppler sweep velocity (15 cm/s) was used, the wall motion filter was 300 Hz and Doppler gain was reduced to clearly differentiate the tricuspid valve (TV) and pulmonary valve (PV) clicks.

For RMPI, two separate Doppler waveforms were obtained in two separate planes (fig. 1). First, the Doppler gate was placed at the tips of the TV leaflets in the apical four-chamber view to measure the tricuspid inflow for the ‘a’ time (TV closure click to the of TV opening click). Then, the Doppler gate was placed at the PV in the short-axis view or in a novel sagittal plane, where the main pulmonary artery and its continuation into the descending aorta is seen, to measure the right ventricular outflow for the ejection time or ‘b’ interval (PV opening click to PV closure click). For RMPI, isovolumetric times (isovolumetric contraction time and isovolu-

Fig. 1. RMPI anatomical planes: the tricuspid inflow, with the Doppler gate at the tips of the TV leaflets in the apical four-chamber view (a), the pulmonary outflow, with the Doppler gate at the level of the PV in the short-axis view (b) and the pulmonary outflow in a sagittal plane, with the Doppler gate at the level of the PV (c).

metric relaxation time) cannot be measured individually, and the ‘a’ interval is a period representative of isovolumetric times and ejection time. The cumulative isovolumetric time (isovolumetric contraction time + isovolumetric relaxation time) is calculated as (a – b). The angle of insonation for both tricuspid and pulmonary waveforms was kept below 15° . The tricuspid inflow waveform was displayed below the baseline and the pulmonary outflow waveform above the baseline as shown in figure 2.

The ‘a’ and ‘b’ intervals were measured, in milliseconds, at the ‘original’, ‘reflected’ and ‘peak’ time points as previously described for LMPI [14] and shown in figure 3. In brief, for the ‘original’ time period the caliper was placed just before the echo of each original valve click (which is in the same direction as flow for opening clicks and in the opposite direction to flow for closure clicks), as close as possible to the echo of the click but without any overlapping with the white echo. For the ‘reflected’ time period, the caliper was placed

Fig. 2. The two constituent waveforms of RMPI: the tricuspid inflow waveform and 'a' interval (a), and the pulmonary outflow wave form and 'b' interval (b).

just before the echo of the reflected clicks, which are thinner than original clicks and are seen in the opposite direction to flow for opening clicks and in the same direction as flow for closure clicks. As the TV opening click has no reflected click and the PV opening click only sometimes has a reflected click, the 'a' interval for the 'reflected' method was measured from the beginning of the reflected TV closing click to the beginning of the original TV opening click, and the 'reflected' 'b' interval was measured from the beginning of the original PV click to the beginning of the reflected PV closing click. For the 'peak' time period, the caliper was placed at the apex of the white echo of each valve click (peak of original and reflected clicks match).

Readings were obtained from the three best waveforms per examination and averaged. Time intervals and RMPI were calculated from the chosen waveforms by 1 of 2 experienced examiners (N.M. and A.H.). As for both LMPI and RMPI, we have previously demonstrated high interobserver agreement in time interval and MPI calculation [19]; thus, intraobserver variability only was calculated. RMPI was calculated as $(a - b)/b$. Only subjects with images that had both original and reflected clicks were included in the analysis. Heart rate was calculated during acquisition of the waveforms for the 'a' and 'b' intervals, with overall heart rate calculated as the mean value of 'a' HR and 'b' HR in the included images.

Statistical Analysis

Statistical analysis was performed using SPSS Version 20 (SPSS Inc., Chicago, Ill., USA). Normal distribution of the data was assessed with a D'Agostino-Pearson test. Descriptive statistics were used to describe quantitative outcome variables. Scatter plots were used to assess the relationship between quantitative study and outcome variables. The changes of time intervals ('a' and 'b') and RMPI in relation to gestational age and the impact of fetal heart rate on RMPI were assessed using regression analysis. The 5th, 50th and 95th percentiles were calculated for RMPI values ('original', 'reflected' and 'peak') for each of the gestational ages from 17 to 38 weeks (5th and 95th percentiles were calculated as $\text{mean} \pm 1.645 \times \text{SD}$). Linear regression equations for gestational age and (1) RMPI ('original', 'reflected' and 'peak') and (2) 'a' and 'b' time intervals ('original', 'reflected' and 'peak') were constructed. One-way ANOVA was carried out to compare the 'original', 'reflected' and 'peak' RMPI values for the representative gestational age. Intraclass correlation coefficients (ICCs) and 95% CI were used to assess the intraobserver variability of the 'original', 'reflected' and 'peak' RMPI.

The sample size, using the statistical model described by Royston [43] for restricting the standard error of the limits of the reference range, was calculated to be 235.

Fig. 3. Measurement of RMPI at the beginning of original valve clicks ('original'), at the beginning of reflected TV and PV closure clicks ('reflected') and at the peak of valve clicks ('peak'). 1: 'Original': 'a' = 258 ms, 'b' = 176 ms and Mod-MPI = 0.47. 2: 'Reflected': 'a' = 249 ms, 'b' = 176 ms and Mod-MPI = 0.41. 3: 'Peak': 'a' = 251 ms, 'b' = 178 ms and Mod-MPI = 0.41.

Results

264 women were chosen for trial inclusion between March 2010 and March 2013. Twelve patients were excluded from final data analysis due to discordant 'a' and 'b' heart rates, and 17 were excluded due to inability to acquire waveforms for all three valve clicks, ('original', 'reflected' and 'peak'), leaving 235 study subjects for analysis. 95% of the patients had similar heart rates measured from TV and PV waveforms, and we could acquire waveforms for all three valve clicks in 94% of subjects, resulting in 89% overall feasibility of acquisition. Results for the

Australian reference range are shown in figure 4 and on-line supplementary figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000362388) for RMPI and 'a' and 'b' time intervals across gestation. Both the 'a' and 'b' constituent time intervals and resultant RMPI showed a modest, progressive increase throughout gestation: from 0.50 ± 0.05 at 19 weeks to 0.57 ± 0.10 at 37 weeks ($\text{RMPI} = 0.421 + 0.004 \times \text{gestational week}$) for 'original' RMPI, from 0.42 ± 0.02 at 19 weeks to 0.51 ± 0.08 at 37 weeks ($\text{RMPI} = 0.373 + 0.004 \times \text{gestational week}$) for 'reflected' RMPI and from 0.43 ± 0.03 at 19 weeks to 0.52 ± 0.09 at 37 weeks ($\text{RMPI} = 0.371 + 0.004 \times \text{gestational week}$).

week) for 'peak' RMPI. Means $\pm$ SD, regression equations and repeatability (intraobserver) for constituent time intervals and resultant RMPI for the three caliper placements are shown in table 2, with good repeatability seen for all measures: 'original' = 0.86 (95% CI: 0.83–0.89), 'reflected' = 0.84 (95% CI: 0.81–0.87) and 'peak' = 0.89 (95% CI: 0.87–0.91).

Table 3 show the 5th, 50th and 95th percentile for RMPI and 'a' and 'b' time intervals at 'original', 'reflected' and 'peak' RMPI from 18 to 37⁺⁶ weeks of gestation. Insufficient cases at 17–17⁺⁶ weeks of gestation precluded their inclusion. 'Original', 'reflected' and 'peak' RMPI showed a slight but statistically significant decrease with increasing fetal heart rate (online suppl. fig. S2) between 130 and 160 bpm: 0.54–0.52 for 'original' RMPI ($R^2 = 0.003$), 0.48–0.46 for 'reflected' RMPI ($R^2 = 0.006$) and 0.50–0.47 for 'peak' RMPI ($R^2 = 0.01$).

When using ANOVA with repeated measures with the Greenhouse-Geisser correction, the mean scores for 'original', 'reflected' and 'peak' MPI were statistically significantly different ($p < 0.0005$). Post hoc tests using the Bonferroni correction revealed a statistically significant difference between 'original' and both 'reflected' and 'peak' ($p < 0.0005$) as well as between 'reflected' and 'peak' ($p < 0.0005$). The mean difference was 0.06 (SD $\pm$ 0.05) for 'original' versus 'reflected' RMPI, 0.05 (SD $\pm$ 0.05) for 'original' versus 'peak' RMPI and 0.01 (SD $\pm$ 0.03) for 'reflected' versus 'peak' RMPI, with all differences being statistically significant ($p < 0.0005$).

Discussion

In this study, we provide prospectively acquired reference intervals for fetal RMPI from 17 to 38 weeks of gestation. Throughout gestation there was a 15–20% increase in RMPI, which has not been noted in previous studies including the only other published study concentrating on reference intervals across gestation for RMPI [30]. There was good, and comparable, repeatability between the three valve closure click methods of measurement, and minimal (albeit statistically significant) effect of fetal heart rate. RMPI waveforms were able to be obtained and RMPI could be calculated and used in 89% of enrolled subjects despite strict criteria for waveform acquisition and use.

In most previously published RMPI literature, the normal fetuses were predominantly acting as internal controls for pathological studies and demonstrated considerable variability in RMPI values. These variations may be

Fig. 4. Effect of caliper position on the calculated RMPI throughout gestation. 5th = 5th percentile; 50th = 50th percentile; 95th = 95th percentile.

Table 2. Summary of results: time intervals and RMPI

Variable	'Original' RMPI	'Reflected' RMPI	'Peak' RMPI
'a' Interval			
Mean $\pm$ SD, weeks	256.73 $\pm$ 15.8	250.44 $\pm$ 15.8	251.49 $\pm$ 15.7
Regression equation	'a' = 225.571 + 1.084 $\times$ GA	'a' = 218.516 + 1.110 $\times$ GA	'a' = 221.533 + 1.042 $\times$ GA
Repeatability	0.92 (95% CI: 0.90–0.94)	0.88 (95% CI: 0.85–0.90)	0.93 (95% CI: 0.92–0.95)
'b' Interval			
Mean $\pm$ SD	168.06 $\pm$ 9.63	170.166 $\pm$ 9.89	169.95 $\pm$ 9.83
Regression equation	'b' = 159.372 + 0.302 $\times$ GA	'b' = 159.945 + 0.355 $\times$ GA	'b' = 162.113 + 0.273 $\times$ GA
Repeatability	0.91 (95% CI: 0.89–0.93)	0.92 (95% CI: 0.91–0.94)	0.93 (95% CI: 0.91–0.94)
RMPI			
Mean $\pm$ SD	0.53 $\pm$ 0.10	0.48 $\pm$ 0.010	0.48 $\pm$ 0.10
Regression equation	RMPI = 0.421 + 0.004 $\times$ GA	RMPI = 0.373 + 0.004 $\times$ GA	RMPI = 0.371 + 0.004 $\times$ GA
Repeatability	0.86 (95% CI: 0.83–0.89)	0.84 (95% CI: 0.81–0.87)	0.89 (95% CI: 0.87–0.91)

Repeatability is expressed as ICC and 95% CI. GA = Gestational age.

due to a number of factors, including studies performed prior to introduction of the use of valve clicks to improve repeatability, differences in machine settings or techniques, differing populations under study, small sample size leading to bias, or possibly maternal characteristics and/or inappropriate inclusions of complicated pregnancies in a unit's 'normal range'. For example, the largest single-center normal range RMPI series published to date, that of Ghawi et al. [35], used retrospective review of fetal echocardiograms performed for a variety of indications, including a large proportion of diabetic pregnancies.

To minimize variability in RMPI measurement and interpretation between centers, adoption of uniform and strict criteria for both waveform acquisition and time interval calculation would be ideal. Using the technique and wall settings derived from Hernandez-Andrade et al. [4], with the modification of fixing wall motion filter at 300 Hz and angle of insonation $<15^\circ$ used in our previous LMPI repeatability study [11], we have produced RMPI reference interval measurements with ICCs of 0.84–0.89 for our three different methods, comparable to our ICCs for LMPI [14]. This suggests that despite the potential for inaccuracy of RMPI because of the need for two-plane image acquisition, RMPI can be a highly reproducible measurement when strict criteria are followed.

Despite the techniques employed in this study to maximize the accuracy of RMPI, standard deviation was wider for RMPI than in our previously published LMPI cohort [14]. This has been previously observed by other authors who have studied both right and left MPIs [27,

30–32]. It is most likely secondary to the variability generated by measuring two separate waveforms and could impact on clinical utility of RMPI if differences between complicated pregnancies and reference intervals are small.

Given fetal right heart dominance and the propensity of the fetal right heart to show an earlier structural and functional response to stress than the left [17], RMPI is likely to be of greatest utility in conditions where the right heart is a predominant feature, such as TTTS and severe early-onset intrauterine growth restriction. Szwast et al. [25] found that although RMPI values from controls overlapped with both the increased values in fetuses with congenital cystic adenomatoid malformation and increased values in recipient TTTS twins, the difference in mean values in TTTS recipients was greater and the degree of overlap with controls was lower than for congenital cystic adenomatoid malformation. We therefore suggest that future exploration of pathological subgroup values compared to the RMPI reference interval should focus on those conditions most likely to yield significantly elevated RMPI. Whether RMPI will complement, supplement or be proven to be of negligible additional value compared to other parameters such as tissue Doppler, M-mode and aortic isthmus is uncertain; however, it is being studied by a number of groups [29, 36]. Although it seems unlikely that any single functional fetal echocardiographic technique currently under research will individually revolutionize surveillance of pathological pregnancies, we suggest that RMPI may have a place as a measure available in standard commercial ultrasound machines, as it

Table 3. Normal reference values**a** RMPI at 3 different caliper positions ('original', 'reflected' and 'peak')

n	Weeks of gestation	'Original' RMPI			'Reflected' RMPI			'Peak' RMPI		
		5%	50%	95%	5%	50%	95%	5%	50%	95%
5	18–18 ⁺⁶	0.36	0.48	0.55	0.33	0.42	0.46	0.36	0.42	0.44
6	19–19 ⁺⁶	0.43	0.52	0.55	0.39	0.43	0.45	0.40	0.42	0.48
11	20–20 ⁺⁶	0.42	0.48	0.63	0.37	0.43	0.59	0.38	0.43	0.60
10	21–21 ⁺⁶	0.40	0.50	0.59	0.37	0.43	0.52	0.38	0.43	0.54
14	22–22 ⁺⁶	0.40	0.50	0.64	0.34	0.45	0.58	0.35	0.44	0.62
11	23–23 ⁺⁶	0.39	0.52	0.68	0.36	0.47	0.65	0.38	0.46	0.62
14	24–24 ⁺⁶	0.40	0.51	0.67	0.34	0.47	0.58	0.33	0.47	0.58
13	25–25 ⁺⁶	0.37	0.50	0.77	0.32	0.46	0.69	0.32	0.48	0.72
9	26–26 ⁺⁶	0.40	0.47	0.65	0.37	0.42	0.59	0.37	0.42	0.60
8	27–27 ⁺⁶	0.46	0.53	0.63	0.37	0.47	0.52	0.37	0.48	0.53
10	28–28 ⁺⁶	0.42	0.57	0.70	0.34	0.51	0.61	0.36	0.51	0.61
10	29–29 ⁺⁶	0.42	0.50	0.64	0.36	0.47	0.60	0.37	0.48	0.59
16	30–30 ⁺⁶	0.36	0.52	0.65	0.34	0.46	0.57	0.35	0.46	0.65
20	31–31 ⁺⁶	0.40	0.52	0.72	0.34	0.43	0.66	0.34	0.42	0.69
10	32–32 ⁺⁶	0.43	0.52	0.64	0.38	0.45	0.56	0.38	0.46	0.57
12	33–33 ⁺⁶	0.43	0.54	0.66	0.37	0.51	0.70	0.37	0.51	0.74
11	34–34 ⁺⁶	0.40	0.56	0.73	0.36	0.55	0.65	0.36	0.57	0.64
9	35–35 ⁺⁶	0.41	0.56	0.70	0.37	0.48	0.62	0.37	0.51	0.64
16	36–36 ⁺⁶	0.40	0.55	0.77	0.31	0.48	0.66	0.33	0.49	0.66
17	37–37 ⁺⁶	0.43	0.57	0.71	0.39	0.51	0.63	0.39	0.51	0.65

n = Number of observations.

b 'a' and 'b' time intervals at 3 different caliper positions ('original', 'reflected' and 'peak').

n	Weeks of gestation	Original RMPI						Reflected RMPI						Peak RMPI					
		'a' interval			'b' interval			'a' interval			'b' interval			'a' interval			'b' interval		
		5%	50%	95%	5%	50%	95%	5%	50%	95%	5%	50%	95%	5%	50%	95%	5%	50%	95%
5	18–18 ⁺⁶	232	237	260	160	165	174.4	226	231	253	160.5	168.3	178	227	231	252	160.7	170	177
6	19–19 ⁺⁶	234	241	253	154	164	168.3	228	233	243	158.5	163.3	173	228	233	243	157.2	163	172
11	20–20 ⁺⁶	235	247	273	151	167	176.5	232	241	256	149.8	167.7	178	234	243	270	152.5	168	178
10	21–21 ⁺⁶	235	245	260	158	163	173.3	225	240	253	158.8	166.5	175	228	241	254	160.0	167	176
14	22–22 ⁺⁶	230	252	272	153	168	176.8	224	243	267	156.8	168.0	180	224	246	267	153.5	170	180
11	23–23 ⁺⁶	240	249	268	155	166	174.5	232	242	272	156.8	166.0	176	238	243	272	157.2	168	176
14	24–24 ⁺⁶	235	249	264	149	166	177.1	228	242	260	148.5	164.5	178	229	242	261	148.5	167	180
13	25–25 ⁺⁶	239	246	278	146	167	177.6	229	243	269	149.7	169.7	180	231	243	273	148.7	170	181
9	26–26 ⁺⁶	234	252	275	155	169	182.0	235	246	274	161.2	169.0	186	230	249	276	159.7	171	186
8	27–27 ⁺⁶	234	255	274	156	165	178.6	228	249	269	164.6	167.2	182	228	248	270	164.6	168	181
10	28–28 ⁺⁶	246	255	274	154	163	180.4	239	248	272	159.6	166.3	186	242	250	273	160.0	167	185
10	29–29 ⁺⁶	243	263	290	164	175	188.8	240	259	281	161.9	176.3	191	242	262	282	161.9	176	192
16	30–30 ⁺⁶	234	257	275	154	168	187.4	230	251	270	153.6	173.5	189	230	254	272	154.6	172	188
20	31–31 ⁺⁶	230	262	289	162	171	186.1	226	253	283	163.3	170.3	189	227	253	285	162.5	170	184
10	32–32 ⁺⁶	236	259	281	157	170	182.0	229	253	275	162.3	170.8	186	229	257	275	162.3	171	185
12	33–33 ⁺⁶	242	258	277	152	167	183.8	238	253	277	157.3	169.0	185	238	253	277	151.8	167	184
11	34–34 ⁺⁶	249	268	286	155	174	192.7	245	263	282	157.0	173.3	194	241	263	277	158.7	169	193
9	35–35 ⁺⁶	243	259	290	154	172	181.0	238	255	281	158.7	174.0	183	239	255	282	157.5	172	182
16	36–36 ⁺⁶	242	262	287	157	168	185.1	234	254	277	157.5	171.5	190	236	257	278	157.0	171	188
17	37–37 ⁺⁶	242	262	294	154	168	181.9	237	254	282	158.6	170.3	183	238	253	280	151.5	170	183

n = Number of observations.

can be performed by ultrasonographers without requiring extensive additional training and offline analysis.

Differing methods of MPI calculation in previous studies may partly account for the variability of results seen in table 1 and may lead to important variations in time intervals. As shown in figure 3, minimal variations in measuring time intervals resulted in a significant difference in the RMPI value.

For MPI to translate from a research tool to clinical practice, not only must it be theoretically likely that there is a clinically important difference between normality and pathology, but it must be possible for it to be routinely acquired and accurately calculated. It is therefore important to choose a measurement landmark that is attainable by a competent sonographer, identifiable in all technically adequate waveforms and reliably repeatable. We have previously proposed using the peak of the valve clicks for both closure and opening as measurement landmarks [14], as the peak is readily identifiable and closure clicks may have variable thickness, with the variability of the breadth of the original click resulting in variability of the calculated mod-MPI. Such variability was present in this study, with >10% difference between 'original' RMPI and both 'reflected' and 'peak' RMPI. 'Reflected' and 'peak' RMPI means, although different on statistical testing, differed by <2%, which is unlikely to be clinically significant.

Therefore, we propose that either 'reflected' or 'peak' measurements could reasonably be used. Ideally, the thin reflected clicks should be used for calculation; however, as the TV opening usually only shows an original click and the peak of both the original and reflected clicks match (i.e. are at identical time points), the 'peak' method overcomes the inconsistency of the breadth of original

clicks, and we believe it should be adopted for calculation. The potential of the TV opening to be thick and tilted is a drawback of using the 'peak' method for RMPI, but can be solved by careful selection of thinner, straight clicks. In practice we found the 'peak' ICC to be superior to both 'original' and 'reflected' ICC. We acknowledge that measurement from 'peak' does not truly reflect physiological time periods, but we feel that ease of identification and improved repeatability of 'peak' improves the likelihood of fetal MPI undergoing translation from a research tool to a clinical tool and should be adopted.

We conclude that fetal RMPI, using stringent acquisition and measurement criteria, is a reliable reproducible measurement and we have produced a gestational age-adjusted reference range as a platform for future investigation of pathological conditions where RMPI may become abnormal prior to conventional fetal Doppler studies. As minor variations in caliper placement at the valve click will produce significantly different ranges, and ICCs were comparable between the three methods, we recommend that the universally identifiable 'peak' should be used in calculation to overcome the issue of breadth of valve clicks.

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