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Assessment of myocardial performance index in late-onset fetal growth restriction

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ABSTRACT

The aim of this study is to determine whether the myocardial performance index (MPI) is increased in fetal growth restriction (FGR) fetuses and if increased MPI is related to adverse outcomes of FGR. This is a prospective cross-sectional study. Seventy-three late-onset FGR fetuses and 97 gestational-age matched control fetuses were enrolled in this study. Fetal blood flow parameters including MPI values were measured and compared between the two groups. For the effect of severity of growth restriction on MPI value, they were also compared with < 3^{rd} and 3^{rd} – 10^{th} centile groups. FGR fetuses were divided into two groups by favorable and adverse outcome and ultrasound parameters were compared between these two groups. Moreover, significant factors related to adverse outcomes by univariate analysis were analyzed by multivariate logistic regression analysis. Pulsatility index of umbilical arterial flow (UA-PI), MPI and amniotic fluid index in the FGR were significantly different from the control fetuses. However, no significant difference between < 3^{rd} and 3^{rd} – 10^{th} centile groups was detected in MPI and UA-PI. The increased levels of MPI and UA-PI were independently related with adverse outcome of late-onset FGR pregnancy. In conclusion, MPI values were increased in late-onset FGR pregnancy, and the higher level of MPI could predict adverse outcome as well as the measurement of UA-PI. Clinicians should consider cardiac dysfunction in FGR through increased MPI.

Keywords: UA-PI, DV-PI, MCA-PI, outcome

Abbreviations:
DV: ductus venosus
EFW: estimated fetal weight
FGR: fetal growth restriction
MCA: middle cerebral artery
MPI: myocardial performance index
UA: umbilical arterial flow
PI: pulsatility index

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INTRODUCTION

Fetal growth restriction (FGR) is a severe problem with a high prevalence of about 19% of live births in low and middle income countries and reportedly, 22% of neonatal deaths occurred in FGR pregnancies.[1] Thus, improvement of management for FGR pregnancies is required to decrease neonatal deaths in the low and middle income countries. FGR has an adverse effect on cardiovascular function,[2] and prenatal cardiovascular remodeling can lead to an increased risk of morbidity and mortality.[3]

Myocardial performance index (MPI), the measurements of the isovolumetric and ejection times, was firstly proposed for adult patients with dilated cardiomyopathy[4] and modified MPI has been established for evaluation of fetal cardiac function in complicated pregnancies by improving the reproducibility of measurements.[5] Recently, several studies have investigated the utility of MPI in FGR fetuses, however the results are controversial.[6,7,8,9,10]

The aim of this study was to compare MPI values between FGR and normal growing fetuses and determine whether the MPI values are related to severity of growth restriction or adverse outcomes in FGR, in Vietnam as one of middle income countries. We also assessed other Doppler parameters in addition to MPI.

MATERIALS AND METHODS

Study design

This is a prospective cross-sectional study conducted at the Department of Obstetrics and Gynecology of Hue University of Medicine and Pharmacy, a tertiary center in central Vietnam, between May 2016 – May 2017.

Patient selection

Seventy-three singleton fetuses diagnosed > 32 weeks as FGR (late onset FGR), an estimated fetal weight (EFW) below the 10^{th} percentile according gestational age, were enrolled as the FGR group. FGR fetuses diagnosed ≤ 32 weeks were excluded, because of their limited number. The FGR group was divided into subgroups: estimated fetal weight (EFW) <3^{rd} (n = 50) or 3^{rd} – 10^{th} (n = 23) centile. The control group consisted of 97 singleton pregnant women with normally grown fetuses, gestational age matched to the FGR group. All cases with maternal diabetes are excluded from this study. All cases with known aneuploidy, multiple anomalies, and cardiac anomaly were excluded. No case with aortic regurgitation or arteriovenous shunt was included. Cases without unavailability of perinatal outcome data were also excluded. Clinical characteristics including maternal age, body mass index (BMI), parity, and weight gain duration pregnancy were collected from medical records. The perinatal outcome data were also collected, including intrauterine fetal death (IUFD), gestational weeks at birth, birth weight, mode of birth, sex of neonates, Apgar scores at 1 min and 5 min, and duration of neonatal intensive care unit (NICU). The fetuses in the FGR group were selected to adjust gestational weeks at birth (n = 57) and was further divided into the favorable (n = 28) and adverse outcome (n = 29) groups. Composite adverse pregnant outcome was defined as cases with one or more factors as below: IUFD, Apgar score < 7 at 1 min or 5 min, need for respiratory support, neonatal infection, preterm birth, and NICU admission.

Ultrasound evaluation

Gestational age was determined based on the first day of the last menstrual period or first trimester ultrasound assessment. Estimated fetal weight (EFW) was calculated by Hadlock's mathematical formulae based on fetal biometric parameters.[11] The < 3rd centile threshold and 3rd – 10th centile threshold were determined according to the standards.[12] Both FGR and controls underwent with ultrasound system WS80A with Elite (Samsung Healthcare, Gyeonggi-do, Korea) including EFW and standard other Doppler parameters together with MPI by two experienced obstetricians. The measurement was started from the diagnosis of FGR to the delivery at least once a week in the FGR group. The values measured at the closest date to birth were collected to be analyzed. In the control group, the subjects who were measured at the matched gestational weeks as the FGR were collected. Standard other Doppler parameters included measurement of the pulsatility index (PI) of UA, middle cerebral artery (MCA) and ductus venosus (DV). Left MPI was obtained as described previously.[5] Briefly, at the chest cross-section and apical four-chamber view, Doppler sample gate was adjacent to the lateral wall of the fetal ascending aorta, close to the mitral valve (MV). The isovolumetric contraction time (ICT) was measured from the closure of the MV to the opening of the aortic valve (AV), the ejection time (ET) from the opening to the closure of the AV, and the isovolumetric relaxation time (IRT) from the closure of the AV to the opening of the MV. MPI was calculated as follows: MPI = (ICT + IRT)/ET. Those measurement were conducted within 7 days of birth.

Statistical analysis

Data was analyzed using the IBM SPSS Statistic 27 statistical package (IBM, New York, USA). Results are shown as number (percentage), mean ± standard deviation (SD), or median [interquartile range]. For the analysis, maternal and neonatal characteristics were compared using Pearson's chi-squared test for categorical variables and Student's *t* test or the Mann-Whitney *U* test for continuous variables according to normal or non-normal distributions, respectively. To determine the independent risk factors for adverse outcomes, multiple logistic regression analyses were performed. Receiver operating characteristic (ROC) curves and cut off values were calculated using JMP® 14 (SAS Institute Inc., Cary, NC, USA). Differences were considered significant with probability values of <0.05.

RESULTS

The evaluation of fetal circulation by doppler parameters

Clinical characteristic differences between the control and late-onset FGR (FGR) groups are summarized in Table 1. Maternal characteristics including age, BMI, nulliparity, and gestational weeks at assessment of the ultrasound parameters were almost similar between two groups. Weight gain during pregnancy in the FGR group was significantly lower than that in the control group ($p < 0.01$). Gestational weeks at birth ($p = 0.047$), birth weight ($p < 0.01$), and Apgar scores at 1 min ($p < 0.01$) and 5 min ($p = 0.01$) in the FGR group were significantly lower than those in the control group. The prevalence of respiratory support, NICU admission of more than 7 days, and neonatal infection in the FGR group were significantly higher than those in the control group ($p < 0.01$). The percentage of IUFD in the FGR group was 1.4 %, but no significant difference was detected in the two groups. Sex of neonates was similar in the two groups.

Table 1 Clinical maternal characteristics and neonatal outcomes

	Control n = 97	**FGR** n = 73	*p*
Maternal characters			
maternal age, years	28.0 [25.0 – 30.0]	27.0 [23.5 – 30.5]	0.205
BMI	19.5 [18.1 – 21.7]	19.7 [17.9 – 21.6]	0.889
nulliparity	53 (54.6)	47 (64.4)	0.201
gestational weeks at assessment	39.0 [37.0 – 39.5]	39.0 [37.0 – 40.0]	0.249
weight gain during pregnancy	13.0 [11.0 – 16.0]	10.0 [7.0 – 13.0]	< 0.01
Pregnant outcomes			
IUFD*	0 (0.0)	1 (1.4)	0.429
preterm delivery	0 (0.0)	15 (20.5)	< 0.01
cesarean section	48 (49.5)	44 (60.3)	0.162
Neonatal outcomes			
gestational weeks at birth	39.0 [38.0 – 40.0]	39.0 [37.0 – 40.0]	0.047
birth weight, g	3100 [2900 – 3400]	2300 [2000 – 2500]	< 0.01
sex of neonate, male	55 (56.7)	33 (45.2)	0.138
Apgar score at 1 min	8 [8 – 8]	8 [7 – 8]	< 0.01
Apgar score at 5 min	9 [9 – 9]	9 [8 – 9]	0.01
Respiratory support	0 (0.0)	21 (28.8)	< 0.01
NICU ≥ 7 days admission	0 (0.0)	18 (31.6)	< 0.01
neonatal infection	0 (0.0)	12 (16.4)	< 0.01

Data are shown as median [interquartile range] and *p* values were calculated using the Mann Whitney *U* test as appropriate for continuous variables.
Data are given as number (%) and *p* values were calculated using the Pearson's chi-squared test or *Fisher's exact test as appropriate for categorical variables.
FGR: fetal growth restriction
BMI: body mass index
IUFD: intrauterine fetal death
NICU: neonatal intensive care unit

The doppler parameters including MPI, UA-PI, MCA-PI, DV-PI and cerebroplacental ratio (CPR) were compared between the control and FGR groups (Fig.1). MPI value in the FGR was significantly higher than that in the control ($p < 0.01$). UA-PI value in the FGR was also significantly higher than that in the control ($p < 0.01$). CPR and amniotic fluid index (AFI) in the FGR were also significantly lower than those in the control ($p < 0.01$), although no significant difference between groups was detected on MCA-PI and DV-PI values.

The relationship of growth restriction severity with MPI value

To evaluate the involvement of the severity of growth restriction in the MPI value, the FGR group were divided into two sub-groups: EFW of < 3rd centile (severe FGR) and EFW of 3rd – 10th centile (mild FGR) (Fig.2). MPI value in the severe FGR group showed the trend to be higher than that in the mild FGR group, but the difference was not significant ($p = 0.066$). There was no difference in UA-PI in the two groups.

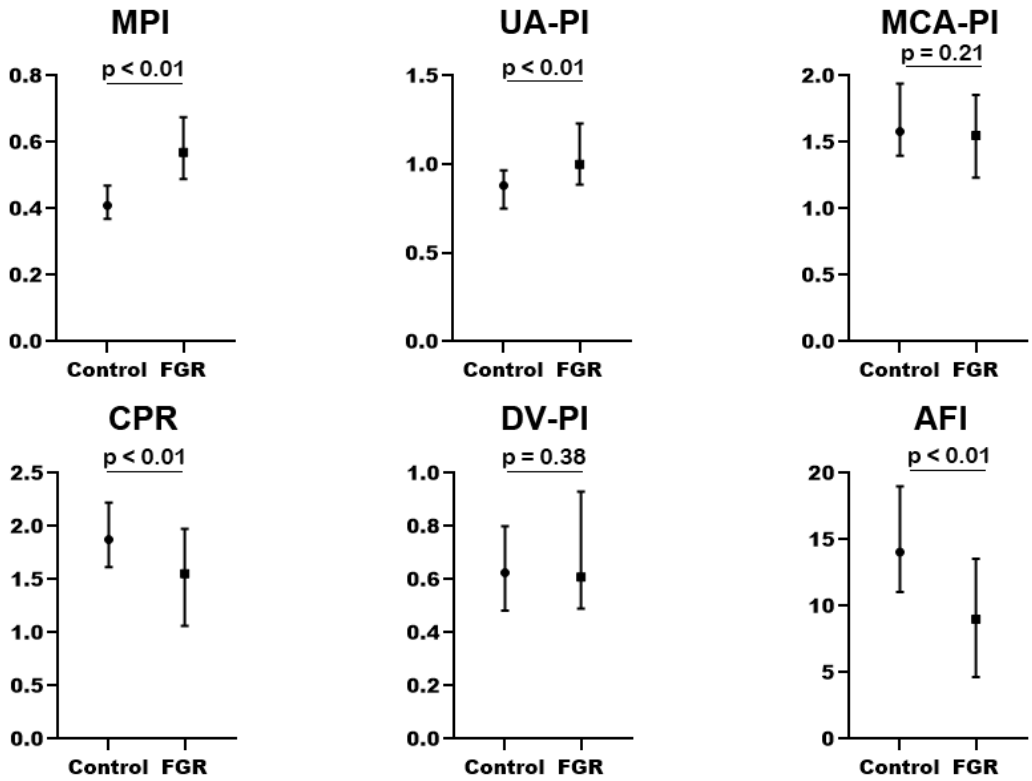

Fig. 1 The comparisons of ultrasound measurements between the control and FGR groups
MPI, UA-PI, MCA-PI, CPR, DV-PI and AFI were compared between the control (n = 97) and FGR (n = 73) groups. The symbols and bars were shown as median and interquartile range, respectively. The p values were calculated using the Mann Whitney U test.
MPI: myocardial performance index
UA-PI: pulsatility index of umbilical arterial flow
MCA-PI: pulsatility index of middle cerebral artery
CPR: cerebroplacental ratio
DV-PI: pulsatility index of ductus venosus
AFI: amniotic fluid index

Risk factors of adverse pregnancy outcome

Several clinical characteristics and fetal blood flow measurements were compared between two subgroups of favorable or adverse pregnancy outcomes (Table 2). There was no significant difference in maternal age, BMI, nulliparity, gestational weeks at measurement, weight gain during pregnancy and sex of neonates. Based on evaluation of fetal well-being using ultrasound, UA-PI and MPI in the adverse outcome group were significantly higher than that in favorable outcome group ($p = 0.01$ and $p < 0.01$, respectively). The prevalence of EFW of < 3^{rd} was also significantly more common in the adverse outcome group, compared with that in the favorable outcome group ($p = 0.035$). However, no significant difference was detected in AFI, MCA-PI and DV-PI values.

A cut-off MPI level of 0.52 has a sensitivity of 89.7%, specificity of 46.4%, and the area under the ROC curve (AUC) was 0.707, which was compatible with the ROC AUC of 0.694 when cut-off UA-PI was 0.99 ($p = 0.936$).

After multiple logistic regression analysis using significant different factors between favorable and adverse outcomes, UA-PI of ≥ 0.99 and MPI of ≥ 0.52 were determined to be independent risk factors of adverse outcome in FGR fetuses (Table 3).

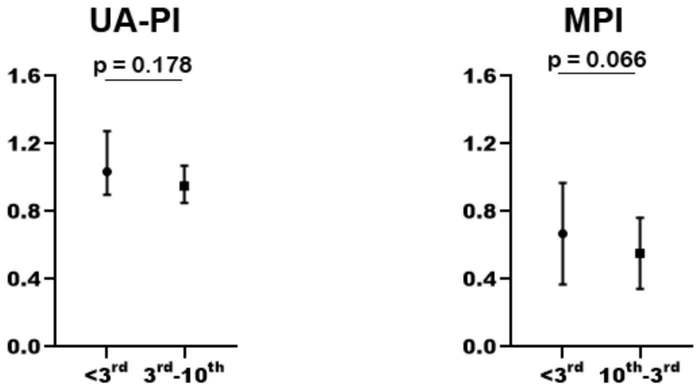

Fig. 2 The comparisons of ultrasound measurements between the severe and mild FGR groups
UA-PI and MPI were compared between < 3rd (n = 50, severe FGR) and 3rd – 10th (n = 23, mild FGR) centile of EFW fetuses. The symbols and bars were shown as median and interquartile range, respectively. The *p* values were calculated using the Mann Whitney *U* test.
UA-PI: pulsatility index of umbilical arterial flow
MPI: myocardial performance index

Table 2 Risk factors of adverse outcome in late-onset FGR pregnancy

	Favorable outcome n = 28	**Adverse outcome** n = 29	*p*
maternal age ≥ 30 years	12 (42.9)	7 (24.1)	0.134
BMI < 19.5 kg/m²	12 (42.9)	16 (55.2)	0.352
nulliparity	17 (60.7)	21 (72.4)	0.349
gestational weeks at assessment	39.0 [38.0 – 39.3]	38.0 [37.0 – 40.0]	0.296
weight gain during pregnancy	9.6 ± 3.3	11.0 ± 4.2	0.183
EFW <3rd	16 (57.1)	24 (82.8)	0.035
AFI	9.3 ± 4.8	11.1 ± 7.3	0.291
UA-PI	0.92 [0.85 – 1.02]	1.05 [0.94 – 1.24]	0.01
MCA-PI	1.52 [1.21 – 2.04]	1.62 [1.38 – 1.80]	0.792
DV-PI	0.54 [0.49 – 0.82]	0.71 [0.51 – 1.13]	0.397
MPI	0.55 [0.38 – 0.64]	0.62 [0.56 – 0.86]	< 0.01
sex of neonate, male	12 (33.3)	12 (41.4)	0.658

Data was shown as number (%) and *p* values were calculated using the Pearson's chi square test for categorical variables. Data was shown as median [interquartile range] and mean ± SD, and *p* values were calculated using the Mann Whitney *U* test and Student *t* test, respectively, as appropriate for continuous variables.
FGR: fetal growth restriction
BMI: body mass index
EFW: estimated fetal weight
AFI: amniotic fluid index
UA-PI: pulsatility index of umbilical arterial flow
MCA-PI: pulsatility index of middle cerebral artery
DV-PI: pulsatility index of ductus venosus
MPI: myocardial performance index

Table 3 Odds ratios of adverse outcome by multiple logistic regression analysis

	odds ratio	95% CI	*p*
UA-PI ≥ 0.99	4.50	1.35 – 15.06	0.015
MPI ≥ 0.52	5.96	1.36 – 26.12	0.018

CI: confidence interval
UA-PI: pulsatility index of umbilical arterial flow
MPI: myocardial performance index

DISCUSSION

The present study firstly demonstrated that MPI values were increased among late-onset FGR fetuses in Vietnam, similarly as previous reports from other countries.[13,14,15,6,7] The mean value of MPI for FGR in this study was compatible with that in the previous report.[7,6] Moreover, MPI showed higher values in the severe FGR (< 3rd of EFW) than that in the mild FGR (3rd – 10th of FGR), although difference was not significant. UA-PI and AFI showed significant differences in the FGR and the control groups, but those were similar between severe and mild FGR groups. Severity of growth restriction had some impact on MPI values, but not on UA-PI and AFI. On the other hand, MCA-PI and DV-PI showed no difference between FGR and normal controls. Conversely, prevalence of severe FGR (< 3rd of EFW), UA-PI and MPI values were significantly increased in late-onset FGR pregnancies with adverse outcomes. After multivariate logistic regression analysis, the high values of UA-PI and MPI were independently related with adverse outcomes.

MPI is known to be a useful index of global cardiac function, which shows systolic and diastolic ventricular myocardial performance.[4] Thus, the results of this study suggested that myocardial function deteriorated in FGR fetuses, and that it might worsen in severe FGR fetuses (< 3rd of EFW). MPI calculates as (ICT + IRT)/ET. However, it is also known that fetal heart rate (FHR) had no effect on the MPI, but the duration of IRT, ICT and ET decreased when FHR increased within normal range.[16] Therefore, MPI might be a clinical useful index in reproducibility than ICT. The sensitivity (79.3%) and specificity (50.0%) to detect adverse effect of ICT (cut off value of 40.0) was as similar as those of MPI (p = 0.566). Therefore, we focused on MPI in this study. MPI was independently involved in the adverse outcome of FGR, and myocadiac dysfunction could have adverse effects on the prognosis of FGR. However, in this study, adverse outcome was only a short-term prognosis, and there were no cases of neonatal death and only three IUFDs. Thus, the prognosis of FGR in this study population was not relatively poor, and it should be carefully interpreted. In terms of clinical utility, a higher value of UA-PI was also independently associated with the adverse prognosis, which supports the recent report.[9]

MCA-PI was not significantly different between normal and FGR fetuses, but CPR was significantly increased. Brain sparing effect with decreased MCA-PI are well known in FGR fetuses. However, the recent systematic review suggested that MCA-PI was worse than UA-PI for prediction of prognosis and UA-PI was comparable to CPR for several outcomes of FGR babies.[17] Thus, it seems consistent with the present result. DV-PI was also not significantly different between normal and FGR fetuses in this study. Increased DV-PI is reported to be detected at the last stage of fetal distress compared with other doppler measurements including UA-PI,[18] and is a superior predictor of IUFD of early-onset FGR.[19] The present study population is only late-onset FGR and included a few cases of IUFD. Thus, the results are comparable with the previous report.

Additionally, in this study, maternal weight gain during pregnancy was significantly lower than in the FGR group than in the control group. Inadequate weight gain has been reported to related with risk of FGR,[20] and it is an interesting result. In Vietnam, it has been reported that the high proportion of the pregnant women had multiple concurrent nutrient inadequacies, which is related to poor maternal weight gain.[21] Nutrient inadequacies during pregnancy would have adverse effect on fetal development and cause FGR. Adequate intervention in this population would decrease FGR.

There are several limitations in the present study. Study population was small and from a single center. However, in comparison with other papers, number of patients was comparable. It is related with a bias that there were a few cases with severe prognosis such as death. Thus, these results might be different from the other situation including early-onset FGR or FGR with more severe prognosis. The other report showed no correlations between MPI and perinatal outcome, but most of cases were early onset FGR.[9] Early-onset FGR and late-onset FGR are known to be based on different pathological mechanisms. It might lead to inconsistency, but we had limited cases with early-onset FGR and could not statistically compare the early-onset and late-onset FGR. Therefore, further research on comparison between early-onset and late onset FGR is required to confirm that. However, obstetric doctors should notice that these cases have already started cardiac dysfunction. Thus, evaluation of MPI and UA-PI might be helpful to detect cases of cardiac dysfunction at early stage, although a prospective study is required.

CONCLUSION

MPI values were increased in late-onset FGR pregnancies and appear to be related to the severity of FGR. A higher level of MPI could predict adverse outcomes as well as the measurement of UA-PI in Vietnam. Clinicians should consider cardiac dysfunction in FGR through increased MPI; this might lead to improved management of FGR.

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STATEMENT OF ETHICS

Informed and written consent was obtained from all participants. The study protocol has been approved by the ethics committees at Hue University of Medicine and Pharmacy (H2016/006) and Nagoya University Hospital (2015-0153).

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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