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Evaluation of predictive value of anterior cerebral artery to umbilical artery Pulsatility Index Ratio and its comparison with medial cerebral artery to umbilical artery Pulsatility Index Ratio for FGR and appropriate for gestational age (AGA) fetuses

Mahyar Mohammadifard[1]✉, **Edris Alishahi**[2], **Nasrin Khorashadizadeh**[3], **Alireza Mirgholami**[1], **Gholamreza Sharifzadeh**[4]

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Authors' Affiliation:
[1]Associate Professor, Department of Radiology, Imam Reza Hospital, Birjand University of Medical Sciences, Birjand, Iran
[2]Resident of Radiology, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[3]Department of Radiology, Valiasr Hospital, Birjand University of Medical Sciences, Birjand, Iran
[4]Assistant Professor of Epidemiology, Department of Epidemiology and Biostatistics, Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran

✉**Corresponding author:**
Associate Professor, Department of Radiology, Imam Reza Hospital, Birjand University of Medical Sciences,
Birjand, Iran
Email: mahyarmohammadifard22@yahoo.com

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ABSTRACT

Background: This study is aimed to investigate the anterior cerebral artery (ACA) to umbilical artery (UA) pulsatility index (PI) ratio as a new Doppler parameter in comparison with the medial cerebral artery (MCA) to umbilical artery (UA). *Material and Methods:* This descriptive cross-sectional study was performed on pregnant women aged 24 to 36 weeks referring. Based on ultrasound criteria, the embryos were separated into two groups, the ones appropriate for gestational age (AGA), and the ones small for gestational age (SGA). *Results:* Mean gestational age and fetal weight in the two groups were not found to be statistically different. The difference between the mean RI of the MCA among the two studied groups was significant ($P < 0.05$). Moreover, the difference between the mean PI of the MCA and ACA between the two groups was significant ($P < 0.05$). Comparing the two ratios of CPR and CPR2, a statistically significant difference was observed between these two ratios ($P < 0.05$) so that CPR2 was <1 with a higher frequency than CPR, indicating that CPR 2 is more sensitive than CPR. *Conclusion:* Early detection of FGR can lead to faster and more effective treatment.

Keywords: Doppler ultrasound, Middle cerebral artery, anterior cerebral artery, fetal growth restriction, Umbilical artery.

1. INTRODUCTION

Nowadays, sonography is of special importance in examining the health of the fetus during pregnancy. Ultrasound examinations are mainly performed in relation to growth, weight, placental and fetal circulation, amniotic fluid and fetal abnormalities, as well as fetal distress examination (Tayyar et al., 2014). Distress can manifest itself as intrauterine growth restriction (IUGR), increased vascular resistance, and hypoxia or acidosis (Ghi et al., 2010). IUGR may be caused by infectious agents, chromosomal or genetic abnormalities, congenital malformations or maternal smoking, but in most cases placental insufficiency is a secondary cause. IUGR often causes complications in the third trimester of pregnancy that are associated with symptoms of preeclampsia. Many factors limit intrauterine growth, including maternal factors (Bartsch et al., 2016), certain infections such as toxoplasmosis, Cytomegalovirus (CMV), syphilis, or rubella (Grivell et al., 2009). Fetal and placental factors include chromosomal abnormalities (e.g., Down syndrome) or structural birth defects such as encephalitis (Gaccioli and Lager, 2016). SGA fetuses are classified as those whose birth weight is below the 10th percentile based on their gestational age, and are at higher risk of mortality compared to AGA fetuses (Cunningham FG, 2018).

Doppler ultrasound plays an important role in the diagnosis of FGR and also has the power to determine the time of delivery in some FGRs. Applying a combination of biometrics with the ultrasound of middle cerebral artery (MCA) and the umbilical artery (UA) is the best tool for identifying small fetuses at risk of adverse events. In addition, Doppler ultrasound provides the possibility of evaluating the redistribution of blood flow in the fetal growth restriction (FGR). This process particularly could be specified through the increment of pulsatility index (PI) in the UA and a decrease in the MCA, suggesting an increase in MCA resistance and dilation of cerebral arteries. Vascular resistance in the MCA is lower in FGR embryos than in AGA embryos, leading to increased cerebral blood flow (Levine, 2018). When the Cerebroplacental Ratio of PI of the middle cerebral artery over PI of the umbilical artery is less than one, it is detected to be abnormal. If this ratio is abnormal, it is associated with increased fetal distress at delivery and increased serious interventions in the fetus (Shwarzman et al., 2013). ACA is part of the Willis ring that is connected to each other by the anterior communication artery (ACoA). These arteries supply the medial surface of the cerebral cortex (frontal and peritoneal lobes), part of the frontal and lateral surfaces of the olfactory bulb and the olfactory pathway, the anterior limb of the internal capsule as well as the anterior part of the corpus callosum, and parts of the basal ganglia (part of the caudate and globus pallidus), (Fleischer, 2018). All four major cerebral arteries (anterior, medial, posterior, and internal carotid arteries) undergo vasodilation in the face of chronic hypoxia, and therefore their PI decreases in placental dysfunction (Vollgraff Heidweiller-Schreurs et al., 2018). Doppler for ACA is capable of showing a decrease in PI before changes in MCA and posterior cerebral arteries (PCA), redistributes cerebral blood flow in the there is a specific hypoxia and chronic situation in the frontal lobes.

Recent studies also suggested a better predictive value of ACA PI doppler in predicting perinatal complications compared to Doppler for MCA (Dunn et al., 2017). Therefore, this study is aimed to assess ACA to UA pulsatility index (PI) ratio as a new doppler parameter in comparison with the medial cerebral artery (MCA) to umbilical artery (UA) PI in FGR and suitable for AGA fetuses.

2. MATERIALS AND METHODS

The present study, as a descriptive cross-sectional one was carried out on pregnant women aged 24 to 36 weeks referring to Imam Reza and Valiasr hospitals in Birjand, Iran, during October 2020 to April 2021. Sampling was performed by non-probability sampling and both criterions of inclusion and exclusion were considered for choosing patients in this study. Inclusion criteria included: having informed consent, gestational age between 24 and 36 weeks based on first trimester ultrasound and LMP.

Exclusion criteria included: fetuses with anomalies and incomplete medical records. Based on inclusion criteria, 40 embryos with growth restriction and 120 embryos with appropriate growth were studied during the study period.

Procedure

Based on ultrasound criteria (head circumference, abdomen circumference, femoral bone length and diameter between two parietals), the embryos were classified into two groups including AGA fetuses (weight percent above 10%) and SGA fetus (weight percent less than 10%). Aimed to evaluate PI of MCA, ACA, and UA, the Doppler ultrasound test was performed with Samsung WA80S ultrasound device and Hz5 frequency probe.

Data analysis

The data obtained from the completed questionnaires were statistically analyzed using SPSS statistical software version 23 and t-test, and then expressed in statistical tables and graphs. $P < 0.05$ was considered as significance level.

Ethical considerations

The information of all patients was kept confidential by the project manager. All declarations of Helsinki and ethics research committees of the University of Medical Sciences for medical research were observed. The code of ethics was obtained for the study, IR.BUMS.REC.1399.451.

3. RESULTS

A total of 160 embryos were examined, of which 40 embryos were in the case group (SGA) and 120 embryos were in the control group (AGA). The mean gestational age in the case and control groups was found to be 31.7±3.07 and 31.6 ± 2.9 weeks, respectively (P = 0.913). Comparison of fetal weight was performed in SGA and control groups, weight range in SGA group and control group was 450-2300g (mean: 1324±460.2g) and 3000-630 g (mean: 1760.6 ± 580.7g), respectively (P = 0.062). Regarding the frequency distribution of fetal growth status in both groups of AGA and SGA, the results were obtained in the most frequent group; in the case group, the most common of these were percentiles greater than 5-9%, in which 37 embryos (92.5%) were included. In the control group, the most common of them was 74-51%, where 23 cases (19.2%) were included (Table 1).

Table 1 Frequency of embryonic growth status in case and control groups

Percentage of growth in the SGA group	Frequency	Percent
>5%	2	5%
5%	1	2.5%
%5-9>	37	92.5%
Total	40	100%
Percentage of growth in the control group	Frequency	Percent
10-24%	16	13.3%
25%	7	5.8%
26-49%	18	15%
50%	22	18.4%
51-74%	23	19.2%
75%	12	10%
76-89%	12	10%
90%	10	8.3%
Total	120	100%

The examinations of Doppler ultrasonography were carried out in terms of Doppler resistive index (RI) of MCA, ACA and UA in two groups. The results revealed that the mean resistive index for UA, MCA, and ACA in SGA group were 0.737 ± 0.099, 0.725 ± 0.29 and 0.701 ± 0.056, respectively, while these values were 0.636 ± 0.238, 0.811 ±0.067 and 0.783 ± 0.064, respectively. As shown in Table 2, the differences between he mean RI of the MCA of the two groups was statistically significant (P <0.05) but the mean RI of the UA and the ACA were not statistically significant between two groups (P> 0.05).

Table 2 Evaluation of RI for UA, MCA, and ACA

Resistance Index (RI)	Mean RI of umbilical artery	Mean RI of middle cerebral artery	Mean RI of anterior cerebral artery	Range RI umbilical artery	RI range of middle cerebral artery	RI range of anterior cerebral artery
group SGA	0.737±0.099	0.725±0.29	0.701±0.056	0.6-1.2	0.6-0.85	0.59-0.8
Control group	0.636±0.238	0.811±0.067	0.783±0.064	0.48-0.87	0.6-0.94	0.58-0.95
P-value*	0.469	0.043	0.985	-	-	-

In terms of PI, it was observed in two groups that the mean PI of UA, MCA, and ACA in SGA group were 1.29 ± 0.254, 1.31 ± 0.29 and 1.21 ± 0.238, respectively, whereas these values were found to be 1.03 ± 0.248, 1.86 ± 0.423 and 1.73. 0.414 in the control

group, respectively. As can be seen, the difference between the mean PI of the MCA, and ACA was statistically significant between the two studied groups (P <0.05), but no statistically significant difference was observed in terms of the mean PI of the UA between the two groups (P> 0.05).

Table 3 PI of UA, MCA, and ACA in studied population

Impact Index (PI)	Mean PI of umbilical artery	SD	Mean PI of middle cerebral artery	SD	Mean PI of anterior cerebral artery	SD	Navel artery PI range	PI range of middle cerebral artery	Anterior cerebral artery PI range
group SGA	1.29	0.254	1.31	0.29	1.21	0.238	0.86-2.2	0.9-2.2	0.81-1.7
Control group	1.03	0.248	1.86	0.423	1.73	0.414	0.63-2.06	0.9-3	0.53-3.46
P-value*	0.521		0.001		0.002		-	-	-

In Table 4 and Figure 1, Cerebroplacental Ratio (CPR) was examined as the MCA PI ratio to the UA PI ratio. The mean of CPR in case and control groups was 1.047 ± 0.304 and 1.9, 0.64, respectively. As can be seen, the differences between two groups in terms of the mean CPR was statistically significant (P <0.05); in the SGA group, 21 patients had a CPR less than 1 and 19 patients had a CPR >1 (Figure 1).

Table 4 Mean CPR range in the two groups

	CPR mean	SD	Range	P-value*
group SGA	1.047	0.304	0.55-1.86	0.000
Control group	1.9	0.64	0.5-4.0	

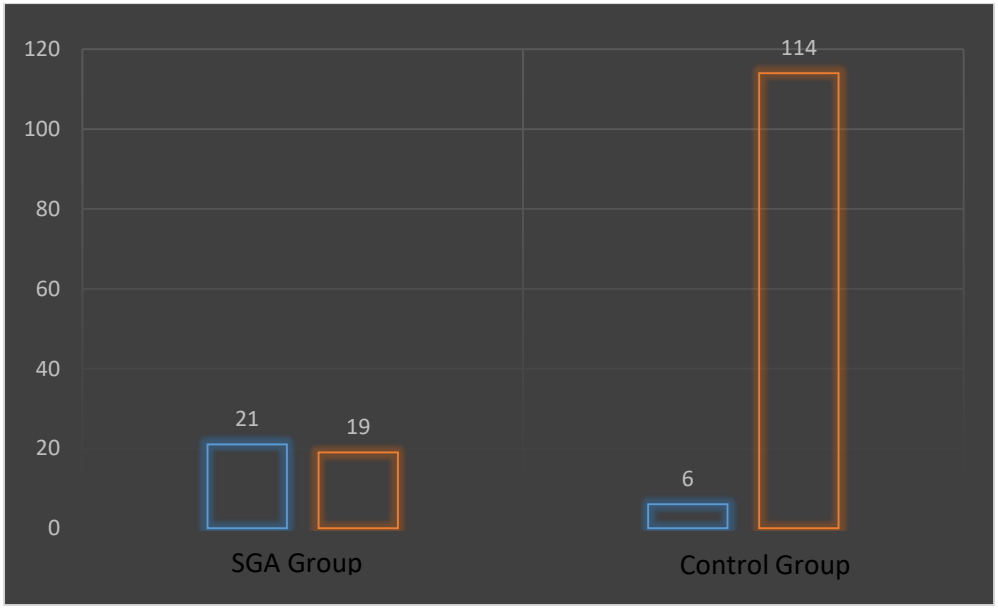

Figure 1 Evaluation of CPR in two groups of SGA and control (Blue: CPR<1; Orang: CPR≥1)

Cerebroplacental ratio 2 (CPR 2) is PI ratio of the ACA to the UA PI ratio. The data from the present study demonstrated that the mean of CPR 2 in SGA and control groups was 0.96 ± 0.28 and 1.75 ± 0.59, respectively. The differences between two studied groups in terms of the mean of CPR 2 was statistically significant (P <0.05). Examination of CPR2 in both SGA and control groups showed that 28 patients had a CPR2 <1 in the SGA group and 12 patients had a CPR2 >1 (Figure 2). In the control group, 104 patients had a CPR2 >1 and 16 patients had a CPR2> 1. The comparison of CPR and CPR2 ratios in the two groups was shown in Table 5, in which the differences between two studied groups was statistically significant (P <0.05).

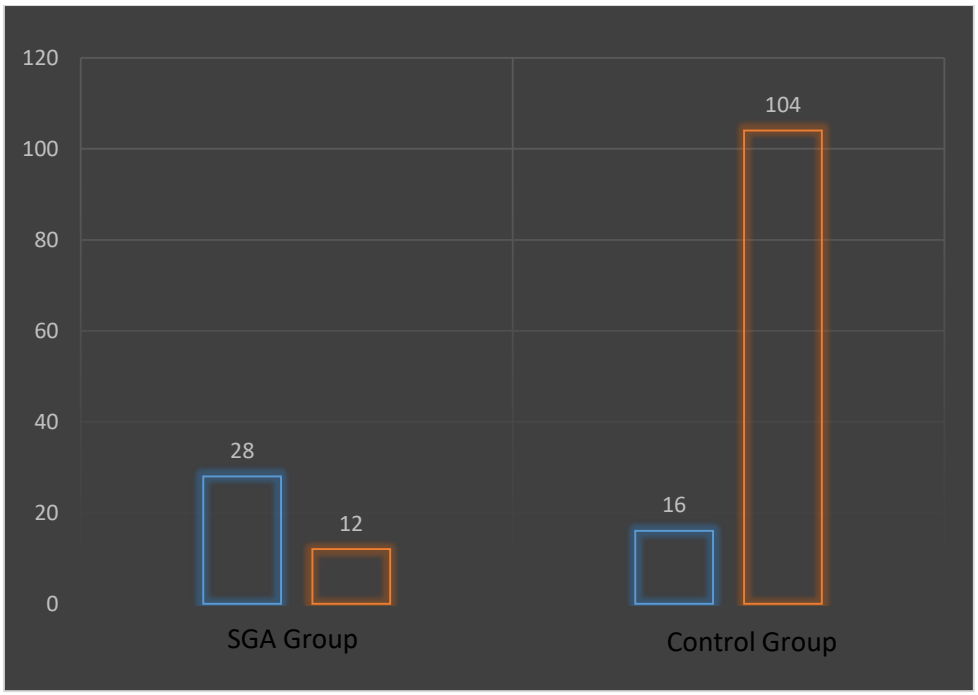

Figure 2 Evaluation of CPR2 in SGA and control groups (Blue: CPR<1; Orang: CPR≥1)

Table 5 Comparison of CPR and CPR2 ratios in the two groups

	CPR<1	CPR2<1	CPR≥1	CPR2≥1	CPR and CPR2 are both less than 1	P-value*
group SGA	21	28	19	12	19	0.035
Control group	6	16	114	104	6	0.002

4. DISCUSSION

FGR has largely replaced the term intrauterine growth retardation. Doppler ultrasound has played a key role in assessing fetal growth status and IUGR pregnancies in recent years (Gomez-Roig et al., 2015). The MCAs are usually the primary option for fetal cerebrovascular Doppler examination due to their more superficial location than other arteries, larger diameter, greater arterial flow, and better angle to the probe (Ebrashy et al., 2005). Thus, the present study is aimed to assess the pulsatility index (PI) ration of the anterior cerebral artery (ACA) to the umbilical artery (UA) as a new Doppler parameter in comparison with the medial cerebral artery (MCA) to umbilical artery (UA) PI in FGR and AGA fetuses.

In our study, the differences between the mean RI of the MCA were statistically significant between the two groups (P <0.05). It's while the differences between the mean RI of the UA and the ACA between the two groups were not statistically significant (P> 0.05). The difference between the mean PI of the MCA and ACA was not statistically significant between the two groups (P <0.05), no statistically significant difference was observed between the mean PI ratio of the UA between the two groups (P> 0.05). In the SGA group, 21 cases with CPR <1 and 19 cases with ≥1 were obtained, while these values were found to be 6 and 114 cases in the control group, respectively. Also, the CPR2 in the SGA group was found to be <1 in 28 cases and ≥1 in 12 cases. In the control group, this ratio was <1 in 16 cases and ≥1 in 104 cases. Comparing the two ratios of CPR and CPR2, a statistically significant difference was observed between these two ratios (P <0.05) so that CPR2 was <1 with a higher frequency than CPR, indicating that CPR 2 is more sensitive than CPR.

Rossi et al., (2017) studied 23 fetuses with FGR and 161 fetuses with normal growth at 24 to 36 weeks of gestation. They reported that the CPR2 curve was linear relative to CPR in the AGA group and had a higher diagnostic value. In comparison with the FGR group, the curve was found to be linear, but the diagnostic coefficient was low due to the limited number of samples. Mentioned study suggested that CPR2 may be a useful clinical parameter in assessing FGR. The data from the present study revealed that the differences between CPR2 and CPR in AGA fetuses were not statistically significant. Moreover, the differences between CPR2 and CPR in SGA fetus was not significantly different, which could be due to the higher number of SGA group samples in comparison with the Rossi study.

A similar study by Kiatsude et al., (2019) showed that the increase in PI in the ACA from 20 weeks and its stability at 32-38 weeks and the decrease in these values after 32 weeks, where it is earlier and more sensitive than the MCA. The results of the present study also demonstrated the PI value of the ACA in the assessment of FGR. The Nosrdan study also identified ACA and MCA were the most sensitive in differentiating the SGA and control groups. PI of UA was the best indicator for determining SGA fetus (Dubiel et al., 1997). This study also showed the value of the ACA index in earlier diagnosis of fetuses for FGR. According to the results of a study by Vandin et al., (1989) the PI ratio in all arteries was significantly reduced in IUGR embryos compared to normal embryos. This study concluded that probably all major cerebral arteries are involved in the brain sparing effect in the presence of chronic fetal hypoxia. The present study also showed the PI value of the ACA and MCA in the diagnosis of fetuses with growth retardation. Oros et al., (2007) suggested ACA as a better indicator (54.5% sensitivity and 73.7% specificity) than MCA (25% sensitivity and 65% specificity) for adverse perinatal outcomes in SGA fetuses with normal UA. They also stated that progressive vasodilation of ACA could increase the risk of adverse perinatal complications. In this study, the value of Doppler examination of the ACA in AGA and SGA embryos was shown when compared with the MCA.

ACA velocimetry was detected to be superior compared to the MCA and PCA as a tool for predicting adverse perinatal outcomes. These outcomes declared that anterior lobes could be protected from the occipital and lateral regions of the fetal brain (Dubiel et al., 2002). Doppler changes in the ACA were shown to be a better indicator than the MCA in the study of FGR. According to this study, the PI ratio of UA in the two groups of normal weight and SGA were not significantly different from each other, but Leavitt showed that abnormal UA Doppler had better sensitivity in predicting SGA and neonatal complications and better specificity against CPR (Leavitt et al., 2021), which could be related to ultrasound techniques, operator skills as well as IUGR stage.

One of the limitations of assessing ACA versus MCA is the presence of the azygous artery and structural abnormalities in the ACA artery relative to the MCA, and the fact that fetal brain Doppler assessment skills require high experience for ACA, although more studies are needed. Fetal MRI, umbilical cord blood and other criteria are needed to show the appropriate diagnostic approach.

5. CONCLUSION

Evaluation and calculation of CPR2 may be an acceptable reflection of FGR that can be detected earlier than CPR. Early detection of FGR can lead to faster and more effective treatment.

Consent for publication

All authors declare that they have Consent for publication

Authors' contributions

All authors contributed to the design of the study, as well as data collection and analysis, and the writing of the manuscript. All authors read and approved the final manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of Birjand University (ethical approval code: IR.BUMS.REC.1399.451).

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Conflict of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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