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Original Article

Foramen Ovale Pulsatility Index as an Early Affected Doppler Study among Abnormal Growth Fetuses: A Recent Insight for Practice Based on a Prospective Study

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What's Known

- Fetal abnormal growth, including fetal growth restriction, and small for gestational age are diagnosed by routine Doppler ultrasonography of the uterine artery, umbilical artery, middle cerebral artery, and ductus venosus pulsatility index.
- However, the role of the foramen ovale pulsatility index study in discriminating them is still unclear.

What's New

- In a prospective study, it was shown that the foramen ovale pulsatility index study could accurately predict fetal growth restriction; however, it had no predictive value in diagnosing small for gestational age.
- Foramen ovale pulsatility index study is suggested as the first-line Doppler study to detect abnormal growth velocity.

Abstract

Background: Routine Doppler study is a common tool for early diagnosis of Fetal Growth Restriction (FGR) and Small for Gestational Age (SGA) patients. It aimed to determine the role of the Foramen Ovale Pulsatility Index (FOPI) study beside routine Doppler study among patients with FGR and SGA fetuses.

Methods: This prospective study was conducted on 35 FGR, 32 SGA, and 33 Appropriate for Gestational Age (AGA) fetuses. Demographic data, amniotic fluid index, neonatal outcome, and Doppler velocimetry, including Umbilical Artery Pulsatility Index (UMAPI), Uterine Artery Pulsatility Index (UTAPI), Middle Cerebral Artery Pulsatility Index (MCAPI), Ductus Venosus Pulsatility Index (DVPI), and FOPI were documented. Kolmogorov-Smirnov normality test, one-way ANOVA, Mann-Whitney U, Kruskal-Wallis, non-parametric pairwise comparisons adjusted for Bonferroni correction, Pearson correlation test, Chi square, Fisher's exact test, and Receiver Operating Characteristic Curve (ROC) analysis with Youden's Index (sensitivity+specificity-1) to estimate cut-off point were used to analyze the data at significance level <0.05 for all tests.

Results: FOPI cut-off points were 2.24 (sensitivity=77%, specificity=94%) and 1.15 (sensitivity=90%, specificity=20%) to predict FGR and SGA, respectively. FOPI showed a positive correlation with UMAPI and UTAPI (r=0.52 and r=0.30, P<0.001 and P=0.006, respectively), but not with MCAPI and DVPI (r=0.08 and r=0.12, P=0.50 and P=0.30, respectively). Besides, UMAPI, UTAPI, and FOPI were altered among patients with stages I and II FGR. Umbilical cord potential hydrogen (umbilical cord pH), 1- and 5-min Apgar score significantly increased by Birth weight centile; however, UMAPI, FOPI, and UTAPI significantly decreased.

Conclusion: UMAPI is recommended to predict short-term neonatal morbidities and demonstrate the early or late onset FGR. Besides, FOPI is suggested as the first-line Doppler study to detect abnormal growth velocity. More studies are warranted, especially considering long-term neonatal morbidities.

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Introduction

Abnormal fetal growth, including Fetal Growth restriction (FGR) and Small for Gestational Age (SGA), affects 10-15% of pregnancies.[1, 2] It is associated with perinatal and neonatal morbidity and mortality, highlighting the importance of early detection and appropriate surveillance of the affected patients. Although the significance of early detection of FGR is established, no uniform practice guideline is present for the definition and diagnosis of FGR.[3] Measuring the height of the uterus fundus from symphysis pubis is a common screening by obstetricians in low-risk pregnancies.[3] Among high-risk pregnancies, fetal abnormal growth can be mainly diagnosed through routine uteroplacental function measured by Doppler ultrasonography, including Uterine Artery Pulsatility Index (UTAPI) and Umbilical Artery Pulsatility Index (UMAPI), as well as by assessing fetus vessel indices s Middle Cerebral Artery Pulsatility Index (MCAPI) and Ductus Venosus Pulsatility Index (DVPI).[4]

Ultrasound accuracy for detecting fetal growth restriction is believed to differ during gestational age.[5] This fact highlights the importance of detecting more indices in FGR. A newly introduced measure is renal artery Doppler, which represents fetal circulation.[6] Since FGR accompanies diastolic dysfunction, it seems that the Foramen Ovale Pulsatility Index (FOPI) is another marker that is affected early in FGR.[7] In this prospective study, the primary goal was to determine the role of the FOPI study besides routine Doppler study among patients with FGR and SGA fetuses. As secondary goals, the possible effect of FOPI on short-term neonatal outcomes, including umbilical cord potential hydrogen (umbilical cord pH), 1- and 5-min Apgar scores, estimated fetal weight, and birth weight, was assessed.

Patients and Methods

Study Design

This prospective study was conducted on 35 fetuses with FGR, 32 fetuses with SGA, and 33 fetuses with AGA recruited in Hafez Perinatology Hospital affiliated with Shiraz University of Medical Sciences from August 2019 to December 2020. All patients provided written informed consent forms, and the research was conducted in compliance with the guidelines set out by the Shiraz University of Medical Sciences Ethics Committee under the reference number IR.SUMS.REC.1399.369. The included patients were 18-35 years old, were at 24-36 weeks of gestation, had singleton pregnancies, and had normal, SGA, or FGR fetuses. They had no underlying diseases, namely overt diabetes mellitus, renal failure, heart failure, thromboembolic diseases, active lupus, obvious fetal anomalies, and fetal heart disease. The women with a history of consumption of medications affecting heart function and smoking were excluded. Moreover, if the stage of abnormal growth changed during routine scans during the pregnancy course, the patient was excluded.

Variable Definition and Measurement

The gestational age was calculated based on the first-trimester scans. Maternal data including age, parity, previous history of abortion, and Body Mass Index (BMI) were recorded as well. One of the measures determined by the sonographic study of the fetuses was the Estimated Fetal Weight (EFW).[8] Besides, the amniotic fluid index (AFI) was evaluated by the sum of the deep pockets of the four uterine quadrants.[9] Color Doppler velocimetry of the FOPI, UMAPI, UTAPI, MCAPI, and DVPI were measured by a sonographer using a GE Voluson E8 ultrasonograph (GE HealthCare, United States). Moreover, the Pulsatility Index (PI) was obtained by Doppler flow analysis using

$$PI = \frac{(maximum\ systoloc\ velocity - minimum\ diastoloc\ velocity)}{mean\ velocity}$$

recorded throughout the cardiac cycle.[10] By normal Doppler studies, fetuses with EFW or abdominal circumference between the 3rd and 10th centiles were labeled as SGA; Delphi FGR criteria included two solitary parameters (abdominal circumference (AC) or EFW<3rd %) and four contributory parameters (EFW or AC<10th) centile; AC or EFW crossing centiles by >two quartiles on growth charts and cerebroplacental ratio <5th % or UA-PI >95th %. In addition, definitions for early- and late-onset FGR in the absence of congenital anomalies, based on international Delphi consensus were defined based on International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) practice guidelines,[11] categorized in table 1 as follows:

FGR patients were categorized into four groups to show the severity of FGR as follows based on the International Society of Ultrasound in Obstetrics & Gynecology.[11]
(increase in level)

Normal: no fetal Doppler abnormalities and / or uterine artery PI>95th centile

Stage 1: UAPI>95th centile and/or cerebroplacental ratio <5th centile

Stage 2: Umbilical artery absence of end-diastolic flow

Stage 3: Umbilical artery reversed end-diastolic flow and/or ductus venosus PI>95th centile or absence of ductus venosus a-wave

Stage 4: Reversed ductus venosus a-wave

Table 1: Definition of early and late fetal growth restriction

Early FGR:	Late FGR:
GA<32 weeks, in the absence of congenital anomalies	GA≥32 weeks, in the absence of congenital anomalies
AC/EFW <3rd centile or UA-AEDF or	AC/EFW<3rd centile Or at least two out of three of the following
1- AC/EFW <10th centile combined with	1- AC/EFW<10th centile
2- UtA-PI>95th centile and/or	2- AC/EFW crossing centiles>2 quartiles on growth centiles*
3- UAPI>95th centile	3- CPR<5th centile or UAPI>95th centile

*Growth centiles are non-customized centiles. AC: Fetal abnormal circumference; AEDF: Absent end-diastolic flow; CPR: Cerebroplacental ratio; EFW: Estimated fetal weight; GA: Gestational age; PI: Pulsatility index; UA: Umbilical artery; UtA: Uterine artery; UAPI:, Umbilical artery pulsatility index.

Finally, AGA was defined by fetal weight and abdominal circumference up to the 10th percentile with normal Doppler indices.[2, 7, 12] The cut-off for dividing FGR into early and late subgroups was 32 weeks of gestation.[13] EFW centiles were calculated using the Hadlock formula by fetal biometry calculator 3.0.1.[14] Moreover, the growth velocity and standard fetal surveillance based on the American College of Obstetricians and Gynecologists was performed for each pregnancy.[15] The patient was disqualified if the abnormal growth stage changed over the course of the pregnancy. Furthermore, the International Society of Ultrasound in Obstetrics and Gynecology standards served as the basis for all sonographic investigations.[16] The pediatric cardiologist followed a standard procedure for doing fetal echocardiography.[7] Fetal foramen ovale blood flow was utilized with pulsed Doppler combined with spatiotemporal image correlation using GE Voluson E8 ultrasonograph (GE HealthCare, United States).[16]

Sample Size Consideration

Based on the information from Nader and others' study,[7] considering type I error=0.05, power of study=95%, two-tailed test, effect size=1.21 (FOPI&FGR mean±SD; 3.70±0.99 and FOPI&AGA mean±SD; 2.77±0.44), 20% attrition, using G*power 3.1.9.2 software tool (developer: Heinrich-Heine-Universität Düsseldorf), the minimum sample size was estimated 100 cases.

Statistical Analysis

Mean±SD, median±Interquartile Range (IQR), and frequency (relative frequency) were used to describe normal quantitative, non-normal quantitative, and qualitative variables, respectively. One-sample Kolmogorov-Smirnov normality test, one-way ANOVA, Mann-Whitney U, Kruskal-Wallis, non-parametric pairwise comparisons adjusted for Bonferroni correction, Pearson correlation test, Chi square, Fisher's exact test, and Receiver Operating Characteristic Curve (ROC) analysis with Youden's Index (sensitivity+specificity-1) to estimate cut-off point were used. G*power 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf) and IBM SPSS version 22 (IBM corporation, USA) software tools were used at a significance level <0.05 for all tests.

Results

The maternal and neonatal characteristics and Doppler and sonographic features of the 100 pregnancies have been presented in table 2.

The study groups were significantly different in terms of UMAPI, FOPI, UTAPI, gestational age at delivery 1- and 5-min Apgar scores, birth weight, umbilical cord pH, birth weight centiles, AC) centiles, GA at ultrasound scan, and EFW centiles. FOPI was the lowest in the AGA, SGA, and FGR groups, respectively. However, there was no discernible difference between the research groups in terms of fetal sex, gravidity, maternal age, maternal BMI, history of abortion, AFI, DVPI, and MCAPI. The frequency of birth weight centiles was significantly different among the FGR, SGA, and AGA groups. All neonates in AGA had birth weight centile more than 10. However, 31.1%, 25.7%, and 37.1% of neonates in the FGR group had birth weight centile less than 3, between 3 and 10, and more than 10, and 0%, 12.5%, and 87.5% of neonates in SGA group had birth weight centile less than 3, between 3 and 10, and more than 10.

The diagnostic values predicting FGR and SGA were evaluated. The related ROC curves are shown in figure 1.

The estimated cut-off point for FOPI predicting FGR was 2.24 with sensitivity=77%, specificity=94%, negative predictive value=94%, positive predictive value=77%, likelihood ratio=12.73, Youden's index=0.71, the area under ROC (AUC)=0.91 (P<0.001, and 95% C.I: 0.84-0.97) with a borderline AUC excellent; The estimated cut-off point for FOPI predicting SGA was 1.15 with sensitivity=90%, specificity=20%, negative predictive value=90%, positive predictive value=90%, likelihood ratio=1.13, Youden's index=0.09, area under ROC=0.41 (P=0.16, and 95% C.I: 0.30-0.52) with a poor borderline AUC.

Table 2: Comparison of maternal, neonatal, Doppler, and sonographic characteristics among fetal growth restriction, small for gestational age, and appropriate for gestational age groups

Characteristics		FGR group, N=35	SGA group, N=32	AGA group, N=33	P value
Maternal age (year), mean±SD		29.80±6.49	27.56±4.77	29.30±6.35	0.28*
Maternal BMI, mean±SD		27.36±4.81	25.53±3.00	27.39±3.93	0.10*
Gestational age at delivery (weeks), median±IQR		37±20	38±1.25	39±20	<0.001†
Gestational age at ultrasound scan(weeks), median±IQR		33±50	32.5±50	31±6.50	0.04†
Previous abortion, n (%)		10 (28.60%)	5 (15.60%)	7 (21.20%)	0.69^
1st min Apgar score, median±IQR		7±2	9±1	8±1	<0.001†
5th min Apgar score, median±IQR		9±1	10±1	9±1	<0.001†
Umbilical cord pH, median±IQR		7.18±0.09	7.27±0.12	7.25±0.10	<0.001†
Gravidity, n (%)	Prime	13 (37.10%)	19 (59.40%)	9 (27.30%)	0.027^
	Multi	22 (62.90%)	13 (40.60%)	24 (72.70%)	
EFW centile, n (%)	<3	11 (31.40%)	10 (31.30%)	0 (0%)	<0.001$
	3-10	6 (17.10 %%)	5 (15.60%)	0 (0%)	
	≥10	18 (51.40%)	17 (53.40%)	33 (100%)	
Birth weight centile, n (%)	<3	13 (31.10%)	0 (0%)	0 (0%)	<0.001$
	3-10	9 (25.70%)	4 (12.50%)	0 (0%)	
	≥10	13 (37.10%)	28 (87.50%)	33 (100%)	
AC centile, n (%)	<3	32 (91.40%)	0 (0%)	0 (0%)	<0.001$
	3-10	2 (5.70%)	32 (100%)	0 (%)	
	≥10	1 (2.90%)	0 (0%)	33 (100%)	
Male sex, n (%)		19 (54.30%)	19 (59.40%)	18 (54.50%)	0.9^
AFI, median±IQR		10±10	12±4	10±9	0.37†
UMAPI, median±IQR		1.34±0.56	0.9±0.17	0.9±0.29	<0.001†
DVPI, median±IQR		0.48±0.24	0.38±0.27	0.48±0.14	0.50†
MCAPI, median±IQR		2.05±0.72	1.8±0.48	1.92±0.27	0.81†
FOPI, median±IQR		3.02±1.22	1.61±0.79	1.22±0.44	<0.001†
UTAPI, median±IQR		1.19±0.83	0.85±0.30	0.85±0.30	0.005†

n (%): Frequency (relative frequency); FGR: Fetal growth restriction; SGA: Small for gestational age; AGA: Appropriate for gestational age; BMI: Body mass index; umbilical cord pH: Umbilical cord potential hydrogen; AFI: Amniotic fluid index; EFW: Estimated fetal weight; UMAPI: Umbilical artery pulsatility index; DVPI: Ductus venesus pulsatility index; MCAPI: Middle cerebral artery pulsatility index; FOPI: Foramen ovale pulsatility index; UTAPI: Uterine artery pulsatility index; *One- way ANOVA test; †Kruskal-Wallis test; ^Chi square test; $ Fisher's exact test

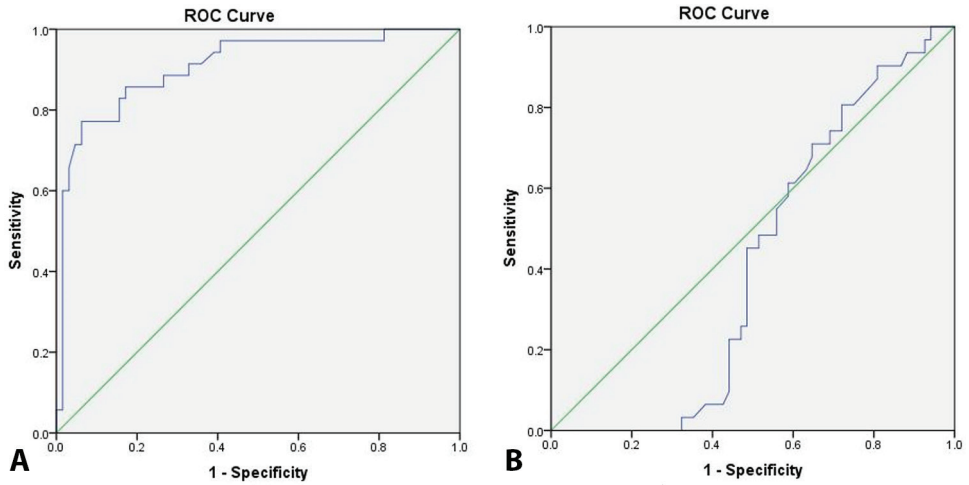

Figure 1: The receiver operating characteristic curve of 100 foramen ovale pulsatility index predicting (A) fetal growth restriction and (B) small for gestational age. ROC Curve: Receiver operating characteristic curve

In the FGR group, positive correlations were observed among EFW, birth weight, and umbilical cord pH (r=42, 0.75; P=0.01, P<0.001), EFW, birth weight, and 1-min Apgar score (r=0.53, 0.79; P=0.001, P<0.001), and EFW, birth weight, and 5-min Apgar score (r=0.48, 0.78; P=0.003, P<0.001). However, negative correlations were detected among umbilical cord pH, 1-min Apgar score, and 5-min Apgar score (r=-0.47, -0.60, -0.54; P=0.004, P<0.001, P<0.001). On the other hand, the results showed no correlations among umbilical cord pH, 1-min Apgar score, 5-min

Apgar score, and FOPI, MCAPI, DVPI, UTAPI, and AFI. Pairwise comparisons of FGR, SGA, and AGA groups concerning UMAPI, FOPI, UTAPI, 1- and 5-min Apgar scores, birth weight, and umbilical cord pH are presented in table 3.

The FGR group had substantially lower medians of birth weight, umbilical cord pH, and 1- and 5-min Apgar scores as compared to the AGA and SGA groups. When comparing the FGR group to the SGA and AGA groups, the UMAPI median was greater in the former. However, no significant difference was observed among SGA and AGA groups. The median of FOPI was significantly higher in the FGR group than in the AGA and SGA groups; furthermore, the median of FOPI was significantly higher in the SGA group than in the AGA group. The median of UTAPI was higher in the FGR group than in the AGA and SGA groups. Nonetheless, no significant difference was found between the AGA and SGA groups in this regard. Regarding 33 patients in AGA (reference category), 32 patients in SGA, and 35 patients in FGR groups, for every unit increase in FOPI the odds of SGA were 3.61 times higher than that of AGA group (95% C.I: 1.23-10.64, P=0.02), similarly for every unit increase in FOPI the odds of FGR was 29.56 times higher than that of AGA group (95% C.I: 7.96-109.77, P<0.001).

In figure 2, the Pearson Correlation test of FOPI showed a positive correlation with UMAPI (r=0.52, P<0.001) and UTAPI (r=0.30, P=0.006), but not with MCAPI (r=0.08, P=0.50) and DVPI (r=0.12, P=0.30).

UMAPI and UTAPI could predict FOPI with r^2=0.27 and 0.09, respectively. However, DVPI and MCAPI were not correlated to FOPI.

Among the participants with FGR, 74.30% (26/35) were at stage 1, 22.90% (8/35) were at stage 2, and 2.90% (1/35) were at stage 3. One fetus in stage 3 FGR and all fetuses in stage 4 FGR were not eligible to be included in the study and were not considered for analysis. Doppler and sonographic features of the 34 participants with stages I and II FGR are compared in table 4.

The results showed a significant difference among the patients with stages 1 and 2 FGR concerning 1- and 5-min Apgar scores, umbilical cord pH, UMAPI, FOPI, and UTAPI. However, no significant difference was found between the two groups concerning DVPI and MCAPI.

Maternal, neonatal, Doppler, and sonographic characteristics of 35 pregnancies with early and late FGR are compared in table 5.

Based on the results, 1- and 5-min Apgar scores, EFW, and birth weight were higher in the late FGR group than in the early FGR group, while UMAPI was higher in the early FGR group. Nonetheless, no significant difference was observed between the two groups regarding maternal age, maternal BMI, umbilical umbilical cord pH, AFI, DVPI, MCAPI, FOPI, and UTAPI.

Table 3: Comparisons of the UMAPI, FOPI, UTAPI, 1- and 5-min Apgar scores, birth weight, and umbilical cord pH between FGR, SGA, and AGA groups

Feature	Group difference	mean±SEM	P value*
1-min Apgar score	FGR-AGA	-1.28±0.24	<0.001*
	FGR-SGA	-1.25±0.24	<0.001
	AGA-SGA	0.02±0.25	>0.99
5-min Apgar score	AGA-SGA	-0.07±0.21	>0.99
	FGR-SGA	-0.95±0.21	<0.001
	AGA-FGR	0.88±0.21	<0.001
Umbilical cord pH	FGR-AGA	-0.09±0.03	0.004
	FGR-SGA	-0.12±0.03	<0.001
	AGA-SGA	-0.02±0.03	>0.99
Birth weight, mean±SEM	FGR-SGA	-1132.02±74.34	<0.001
	FGR-AGA	-1132.02±74.35	<0.001
	SGA-AGA	-401.86±76.02	<0.001
UMAPI, mean±SEM	SGA-AGA	-0.04±0.51	>0.99
	SGA-FGR	-0.75±0.15	<0.001
	AGA-FGR	-0.72±0.15	<0.001
FOPI, mean±SEM	AGA-SGA	-0.33±0.16	0.04
	AGA-FGR	-1.51±0.15	<0.001
	SGA-FGR	-1.18±0.16	<0.001
UTAPI, mean±SEM	AGA-SGA	-0.11±0.09	0.79
	AGA-FGR	-0.43±0.09	<0.001
	SGA-FGR	-0.32±0.09	0.003

UMAPI: Umbilical artery pulsatility index; FOPI: Foramen oval pulsatility index; UTAPI: Uterine artery pulsatility index; FGR: Fetal growth restriction; SGA: Small for gestational age; AGA: Appropriate for gestational age; umbilical cord pH: Umbilical cord potential hydrogen; Adj. Sig: Adjusted significance; *Mann-Whitney U test; SEM: Standard error of mean

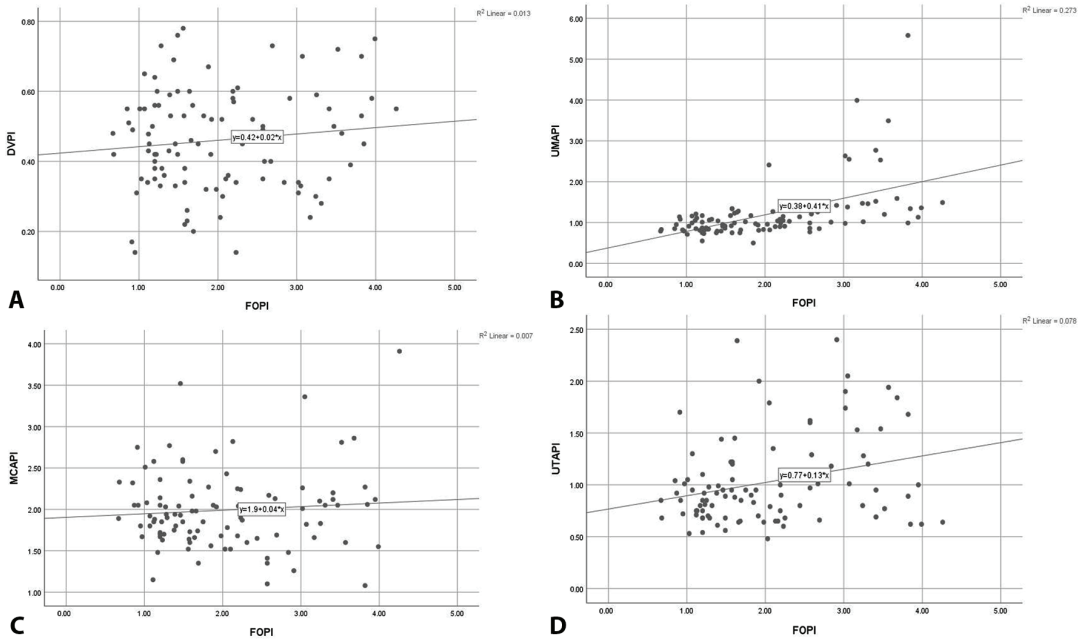

Figure 2: The Pearson correlation of the foramen ovale pulsatility index (FOPI) with ductus venosus pulsatility index (DVPI) (A), umbilical artery pulsatility index (UAPI) (B), middle cerebral artery pulsatility index (MCAPI) (C), and uterine artery pulsatility index (UTAPI) (D).

Table 4: Doppler and sonographic features of the 34 participants with stages I and II FGR

Feature	FGR stage 1	FGR stage 2	P value*
AFI, median±IQR	11.5±6.87	11±80	0.90
UMAPI, median±IQR	0.99±0.32	2.59±1.24	0.009
DVPI, median±IQR	0.45±0.22	0.51±0.35	0.70
MCAPI, median±IQR	1.93±0.42	1.93±0.88	0.70
FOPI, median±IQR	1.61±1.06	3.12±0.51	0.01
UTAPI, median±IQR	0.89±0.35	1.61±0.63	0.006
Umbilical umbilical cord pH, median±IQR	7.19±0.10	7.11±0.17	0.01
1-min Apgar score, median±IQR	8±1	6±1.50	0.008
5-min Apgar score, median±IQR	9±0.75	8±0.75	0.001

FGR: Fetal growth restriction; umbilical cord pH: Umbilical cord potential hydrogen; AFI: Amniotic fluid index; UMAPI; Umbilical artery pulsatility index; DVPI: Ductus venosus pulsatility index; MCAPI: Middle cerebral artery pulsatility index; FOPI: Foramen ovale pulsatility index; UTAPI: Uterine artery pulsatility index; *Mann-Whitney U test

Table 5: The maternal, neonatal, Doppler, and sonographic characteristics of the 35 pregnancies with early and late FGR

Characteristic	Early FGR group, n=17	Late FGR group, n=18	P value*
Maternal age (year), mean±SD	30±7.70	29.6±5.31	0.60
Maternal BMI, median±IQR	27.5±9.5	25.75±8.7	0.70
1-min Apgar score, median±IQR	6±1	8±1	0.002
5-min Apgar score, mean±SD	8±2	9±2	0.02
Umbilical umbilical cord pH, median±IQR	7.16±0.15	7.19±0.10	0.053
EFW, median±IQR	1256±46	1919±55	<0.001
Birth weight, median±IQR	2100±64	2320±41	0.01
AFI, median±IQR	3.17±1.08	2.63±1.21	0.94
UMAPI, median±IQR	1.59±1.49	1.18±9.37	0.002
DVPI, median±IQR	0.5±0.25	0.42±0.19	0.06
MCAPI, median±IQR	1.87±0.67	2.07±0.75	0.96
FOPI, median±IQR	1.49±1.44	2.04±1.13	0.19
UTAPI, median±IQR	1.53±0.83	0.1.01±0.54	0.14

Early Fetal Growth Restriction (Early FGR) was at the gestational age ≤32 weeks; Late Fetal Growth Restriction (Late FGR) was at the gestational age >32 weeks; BMI: Body mass index; umbilical cord pH: Umbilical cord potential hydrogen; AFI: Amniotic fluid index; EFW: Estimated fetal weight; UMAPI: Umbilical artery pulsatility index; DVPI: Ductus venosus pulsatility index; MCAPI: Middle cerebral artery pulsatility index; FOPI: Foramen ovale pulsatility index; UTAPI: Uterine artery pulsatility index; *Mann-Whitney U test

This research demonstrated a substantial difference in the frequency of birth weight centiles across the FGR, SGA, and AGA groups, which may help to assess the potential relationship between birth weight and neonatal outcome. All neonates in the SGA and AGA groups had birth weight centile more than 10; however, 8.60%, 65.70%, and 25.70% of neonates in the FGR group had birth weight centile less than 3, between 3 and 10, and more than 10. Birth weight centiles are compared with EFW centiles, umbilical cord pH, 1-min Apgar score, 5-min Apgar score, UMAPI, FOPI, and UTAPI in table 6.

EFW centiles correlated with birth weight centiles; umbilical cord pH, 1-min Apgar score, and 5-min Apgar score differed in Birth weight centiles, and UMAPI, FOPI, and UTAPI significantly decreased by Birth weight centiles.

Discussion

The results showed the difference of FOPI among AGA, SGA, and FGR groups; besides, UMAPI and UTAPI differed among FGR-AGA and FGR-SGA, but not SGA-AGA. This result can be a new set point for early detection of abnormal growth of a fetus in sonography since it was previously shown that UMAPI is the first Doppler affected in fetuses with AC less than 5th centile.[17] Kiserud and colleagues indicated that FO shunting was impaired among fetuses with FGR, especially premature fetuses, due to decreased FO diameter.[18] In line with them, we increased the FOPI measured for AGA, SGA, and FGR. Considering FOPI as a determining factor, Nader and colleagues conducted a study on patients with FGR and normal controls.[7] They found that individuals with FGR had higher FOPIs and that this was because of left ventricular diastolic dysfunction. The result of their study was that UTAPI and UMAPI were directly correlated to FOPI, while MCA was inversely associated with FOPI, and they introduced 2.95 as the cut-off for FOPI. Nader and others defined FGR as a fetal weight less than the 10th centile with the abnormal Doppler. In line with them, our study showed via Pearson Correlation test a positive correlation of FOPI with UMAPI and UTAPI, but not with MCAPI and DVPI, which is incongruent to them, as they presented inverse association. An explanation may be that we categorized abnormal growth fetuses to SGA and FGR focusing on the importance of FOPI in abnormal growth fetuses since it was abnormal in the SGA group in which all other Doppler were normal. Moreover, 2.24 was the cut-off for FOPI in our study, which is less than the previous

Table 6: Comparison of birth weight centiles with EFW centiles, umbilical cord pH, 1-min Apgar score, 5-min Apgar score, UMAPI, FOPI, and UTAPI in 100 patients

Characteristic		EFW centile, n (%)			P value	Umbilical cord pH, mean±SD	P value	1-min Apgar score, mean±SD	P value	5-min Apgar score, mean±SD	P value	UMAPI, mean±SD	P value	FOPI, mean±SD	P value	UTAPI, mean±SD	P value
		<3	3-10	>10													
Birth weight centile, n (%)	<3	8 (61.50%)	3 (23.10%)	2 (15.40%)	<0.001*	7.06±0.22	<0.001@	6.3±1.38	0.001@	7.69±1.10	<0.001@	1.88±1.03	<0.001@	2.67±0.67	<0.001@	1.42±0.53	<0.001@
	3-10	4 (30.40%)	5 (38.50%)	4 (30.80%)		7.22±0.89		8±0.91		9.46±0.66		1.11±0.32		2.62±0.91		0.98±0.35	
	>10	8 (10.80%)	4 (5.40%)	62 (83.80%)		7.24±0.08		7.22±0.12		9.29±0.75		1.08±0.62		1.77±0.85		0.96±0.37	

n (%): frequency (relative frequency); *Fisher's exact test; @ One way ANOVA test; umbilical cord pH: Umbilical cord potential hydrogen

study. We suppose that this difference is due to our study's different categorization. In our study labeled as SGA, fetuses with normal Doppler were included, but they considered fetuses with abnormal Doppler. It seems that early and late FGRs are different. Baschat presented in a review that UMAPI abnormality shows clinical acceleration among early-onset growth-restricted fetuses that need surveillance with the early presentation.[13] They defined these fetuses as having estimated fetal weight less than the 10th centile beside any impaired Doppler of UMAPI, MCAPI, or cerebroplacental ratio Doppler index. Meler and colleagues introduced UMAPI Doppler as a prognostic tool and presented its deterioration in early onset SGA patients with no clear definition of SGA fetuses.[19] Both mentioned studies presented MCAPI as the most important study in late-onset FGR fetuses. Moreover, Kanagawa and others found MCA alterations after 31 weeks of gestation in the late-onset FGR group, as well as in the early-onset FGR group representing normal umbilical artery Doppler indices.[20] The only statistically different Doppler in early and late FGR groups was UMAPI. Although MCAPI decreased in the FGR group, it was not statistically different among AGA, SGA, and FGR groups.

Another aspect of early and late FGR is the Ductus venosus Doppler study, which is a prognostic tool among patients with early- and late-onset FGR because of showing the fetal acid-base status.[19] DVPI deteriorates in cases of unapparent anomalies and umbilical-placental abnormalities.[20] It is the most trustworthy index to display fetal cardiac function, representing increased resistance in the right atrium.[21, 22] The current study's results revealed no significant differences across various categories and subgroups. We hypothesize that the most severe cases, including patients with stage 2 FGR, are characterized by the absence of ductus venosus impairment.

When studying short-term neonatal outcomes, our study showed statistically different 1- and 5-min APGAR and umbilical cord pH in FGR-SGA and FGR-AGA groups and not SGA-AGA. However, birth weight was different among all these three groups. Moreover, our results were better for fetuses in late-onset FGR rather than early-affected ones with worsened results in FGR stage 2 compared to stage 1. In a recent study, Moraitis and others introduced UMAPI as not effective in predicting neonatal morbidity in low-risk pregnancies.[23] They attributed this result to two facts. First, the analyzed included articles in this systematic review were performed on a population with fetuses having estimated birth weight less than the 10th centile, which was named SGA, and less than the 3rd centile, which was named severe SGA. They found that abnormal UMAPI was detected among 20% of SGA compared to 25% of the severe SGA group. As the second reason, they demonstrated that aberrant growth was not a significant source of newborn morbidity. The lack of integrity among the definitions of growth retardation may cause bias in the interpretation and generalization of studies. In contrast, UMAPI was mentioned by some authors to be associated with perinatal outcomes, including cesarean section delivery, preterm birth, and neonatal intensive care unit admission in terms of respiratory distress, morbidities such as sepsis, hyperbilirubinemia, the incidence of intra-ventricular hemorrhage, and low 5-min Apgar score.[24, 25] In the same line, the present study results show a negative correlation between UMAPI and umbilical cord pH, 1- and 5-min Apgar scores. Heidweiller-Schreurs and others conducted a systematic review and stated that the MCAPI index was not an accurate determining factor of adverse outcomes and Apgar score compared to UMAPI.[26] We agree with their result since we found no correlation between this index and umbilical cord pH and 1- and 5-min Apgar scores. Martinez-Portilla conducted a systematic review and showed UTAPI as a moderately accurate tool to predict the perinatal death in SGA fetuses with different included studies considering SGA as EFW less than 10th, 5th, and 3rd centile, and two standard deviations or decreasing growth over scans.[27] At 30-34 weeks of gestation, Zarean and Shabaninia found unfavorable perinatal outcomes in high-risk fetuses with deficient UTAPI, but not in low-risk pregnancies.[28] It was recently proven that persistently abnormal UTAPI during the third trimester predicts birth weight less than the 10th centile.[29] Contrary to all mentioned studies, we found no association between UTAPI and adverse outcomes. A reason may be attributed to the population study. Zarean and Shabaninia[28] and Ramos and others[29] studied patients with abnormal Doppler rather than abnormal growth fetuses. This result may be different among growth retarded fetuses. DVPI is strongly associated with stillbirth regardless of gestational age,[30] but we had no fetuses with abnormal DVPI, and we did not study this Doppler. We observed improved neonatal umbilical cord pH and 1- and 5-min Apgar in neonates with more birth weight. Furthermore, there was no statistically significant difference between EFW and birth weight, revealing the importance of attention paid to sonographic evaluations during pregnancy.

One of the strong points of the present investigation was that FOPI was explored in addition to the routine indices to determine if it is valuable to detect affected FOPI among abnormal growth fetuses that led to presenting the cut-off for FO measure. Moreover, the patients were categorized into SGA and FGR groups, which could shed light on the clinical consequences of different Doppler abnormalities. This study also took into account the start of growth limitation, which may have an impact on the function and predictive significance of several Doppler indicators. We should consider that measuring each Doppler may have bias dependent on the operator-inserted pressure on probe[31] or the maternal body mass index.[32] One of our study limitations was that in the FGR group involved, the fetuses with impaired ductus venosus in the sampling duration for this study were not referred to our institute by chance. This may be because of the early need for delivery because of the non-reassuring state of the fetuses that automatically led to not being involved in the samples. Furthermore, there was no definite chart for standard measures of foramen ovale Doppler in each gestational age. Moreover, other maternal and neonatal morbidities that might be affected in this population were not considered. Long-term neonatal morbidities were not studied as well. Although these limitations may lead to bias in the interpretation and extrapolation of the results, the findings of this research seem to represent a watershed moment in the identification and care of suspected abnormally growing fetuses.

Conclusion

UMAPI was shown to be an index for predicting neonatal morbidity, which was statistically different among patients with early and late FGR. UMAPI, UTAPI, and FOPI were altered among patients with stages I and II FGR. Umbilical cord pH, 1-min Apgar score, and 5-min Apgar score significantly increased by birth weight centile; and UMAPI, FOPI, and UTAPI decreased by birth weight centile. FOPI was the only diagnostic index for patients with SGA fetuses, which was affected earlier than other indices. Although FOPI was affected by advanced growth restriction, it was not statistically correlated to short-term neonatal morbidities. This implies that FOPI may affect long-term neonatal morbidities, which is suggested to be investigated in further studies, especially considering long-term neonatal morbidities.

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Authors' Contribution

A.F developed the concept, design, literature search, article draft, and data interpretation, and supervised the work; F.GH developed the intellectual content, literature search, and manuscript review, and drafted the article; N.N developed the intellectual content, literature search, data acquisition, result interpretation, manuscript review, manuscript editing, and drafted the article; A.M.SH developed the intellectual content, literature search, data acquisition, result interpretation, and manuscript review, and drafted the article; M.K developed the intellectual content, literature search, data acquisition, result interpretation, manuscript review, and data interpretation, and drafted the article; N.A developed the intellectual content, result interpretation, manuscript review, and data interpretation, and drafted the article; H.V developed the intellectual content, literature search, result interpretation, manuscript review, data interpretation, and manuscript editing, and drafted the article; M.Z developed literature search, data acquisition, statistical analysis, result interpretation, manuscript preparation, manuscript editing, manuscript review, and drafted the article; KH.B developed the intellectual content, manuscript review and drafted the article; Z.O developed the intellectual content, literature search, data acquisition, and manuscript review, and drafted the article. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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