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Fetal Femoral Artery Doppler Evaluation in Late-Onset Fetal Growth Restriction: A Case-Control Study

Geç Başlangıçlı Fetal Büyüme Geriliğinde Fetal Femoral Arter Doppler Değerlendirmesi: Vaka Kontrol Çalışması

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Abstract

Objective: To compare the femoral artery and other ultrasonographic Doppler measurements between fetuses with late-onset fetal growth restriction and uncomplicated fetuses.

Material and Method: This prospective cohort study was conducted with 168 patients, including 83 pregnancies presenting with late-onset fetal growth restriction and 85 uncomplicated control pregnancies at similar gestational weeks. The study group was further divided into two according to the neonatal intensive care unit requirements. Demographic characteristics, obstetric characteristics, femoral artery and other ultrasonographic Doppler measurements, and pregnancy outcomes were compared between the groups.

Results: Uterine artery pulsatility index, umbilical artery systolic/diastolic ratio, and peak systolic velocity of the middle cerebral artery were similar between the study and control groups. However, while the middle cerebral artery pulsatility index was significantly lower in the study group, the femoral artery pulsatility index value was significantly higher ($p<0.001$ and $p=0.002$, respectively). When the two subgroups of the study group were compared according to the neonatal intensive care unit requirements, their femoral artery and other Doppler measurements were similar. Estimated fetal weight was statistically lower in the group requiring neonatal intensive care unit ($p=0.033$).

Conclusion: The femoral artery pulsatility index measurement was higher in the late-onset fetal growth restriction cases than in the healthy controls. The Doppler examination of the femoral artery was not found to be effective in demonstrating adverse perinatal outcomes.

Keywords: Adverse perinatal outcomes, cerebroplacental ratio, femoral artery doppler, fetal growth restriction.

Özet

Amaç: Femoral arter ve diğer ultrasonografik Doppler ölçümlerini geç başlangıçlı fetal büyüme geriliği olan fetüsler ile komplike olmayan fetüsler arasında karşılaştırmak.

Gereç ve Yöntem: Bu prospektif kohort çalışması geç başlangıçlı fetal gelişme geriliği saptanan 83 çalışma grubu gebe ile benzer gebelik haftasına sahip 85 komplike olmayan kontrol grubu gebe dahil olmak üzere 168 hasta ile gerçekleştirilmiştir. Aynı zamanda yenidoğan yoğun bakım ünitesi gereksinimine göre çalışma grubu ikiye ayrıldı. Gruplar arasında demografik özellikler, obstetrik özellikler, femoral arter ve diğer ultrasonografik doppler ölçümleri ve gebelik sonuçları karşılaştırıldı.

Bulgular: Uterin arter pulsatilite indeksi, umbilikal arter sistolik/diyastolik oranı ve orta serebral arterin pik sistolik hızı çalışma ve kontrol grupları arasında benzerdi. Ancak çalışma grubunda orta serebral arter pulsatilite indeksi anlamlı olarak düşük bulunurken, femoral arter pulsatilite indeksi anlamlı olarak yüksekti (sırasıyla, $p<0.001$ ve $p=0.002$). Çalışma grubunda yenidoğan yoğun bakım ünitesi gereksinimine göre iki grup karşılaştırıldığında femoral arter ve diğer doppler ölçümleri benzer izlendi. Tahmini fetal ağırlık, yenidoğan yoğun bakım ünitesi gerektiren grupta istatistiksel olarak daha düşüktü ($p=0.033$).

Sonuç: Geç başlangıçlı fetal büyüme geriliği olgularında femoral arter pulsatilite indeksi sağlıklı kontrollere göre daha yüksekti. Femoral arterin Doppler incelemesinin olumsuz perinatal sonuçları göstermede etkili olmadığı bulundu.

Anahtar Sözcükler: Femoral arter doppler, fetal büyüme geriliği, olumsuz perinatal sonuçlar, serebroplasental oran.

Introduction

Although fetal growth restriction (FGR) is difficult to define, it is basically a pathological growth restriction associated mainly with placental insufficiency (1). For the diagnosis of FGR, estimated fetal weight (EFW) or abdominal circumference (AC) determined by ultrasonography should be less than the 10th percentile for gestational age (2). FGR is associated with an increased risk of perinatal mortality and morbidity, and its incidence has been reported to reach 5.5% in some population-based studies (3). Depending on the gestational age at diagnosis, a broad classification of FGR into early-onset (<32 weeks) and late-onset (≥32 weeks) categories has been proposed. The rationale for this classification is based on the differences in severity, natural disease course, doppler findings, placental findings, and treatments between these two FGR phenotypes (4). Late-onset FGR (LO-FGR) is difficult to detect and is often overlooked. In this phenotype, fetal dimensions may be within normal ranges, and measurable Doppler changes are less prominent (5).

The presence of placental insufficiency in LO-FGR may not be reflected in the Doppler examination of the umbilical artery (UA). Recent studies have shown that Doppler ultrasonography performed in other vascular regions, such as the brain and uterine arteries, may be more important in detecting LO-FGR that cannot be identified through the Doppler examination of the UA (6). In LO-FGR, adaptive changes in the cerebral circulation (brain-sparing effect) occur as a result of low resistance to flow in the middle cerebral artery (MCA) (7). Apart from the formation of brain-sparing effects, there is little literature information concerning the diagnostic and predictive value of the Doppler examination of the femoral artery (FA) among peripheral arteries. Some animal experimental studies have investigated the effects of the Doppler examination of the FA in the presence of hypoxia (8, 9). However, only a few studies have performed the Doppler examination of the FA in patients with FGR (10), and there is still an open debate as to which Doppler parameter indicates a progressive or stable fetal state in LO-FGR cases.

In this study, we investigated the utility of Doppler ultrasonography measurements in the diagnosis of cases with LO-FGR. The primary endpoint of the study was the importance of ultrasonographic Doppler parameters in the diagnosis and follow-up of patients with LO-FGR. The secondary endpoint was the ability of the FA Doppler measurements and other Doppler markers to predict adverse perinatal outcomes in patients with LO-FGR.

Material and Method

This prospective case-control study was conducted from April 2022 to April 2023 at the perinatology clinic of Ankara City Hospital. Written informed consent was obtained from all participants. Research and publication ethics were complied with in our article. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Number 2 Medical Research Ethics Unit of the Ankara City Hospital (Number: E2-22-2674, Date: 26/10/2022).

Study population

The study included 168 cases, including 83 pregnancies presenting with late-onset FGR (LO-FGR) and 85 healthy singleton pregnancies. All pregnancies were past the 32nd gestational week. The LO-FGR cases were further divided into two groups according to the requirement of admission to the neonatal intensive care unit (NICU) (15 with and 68 without this requirement). The control group was selected from pregnant women with similar characteristics in terms of body mass index (BMI) and gestational week. Pregnant women with chronic lung and heart diseases, hypertensive diseases of pregnancy, chronic kidney and liver diseases, systemic diseases, or a history of malignancy were excluded from the study. Furthermore, twin pregnancies and pregnant women with fetal structural and chromosomal disorders were not included in the study. Cases that met the FGR criteria specified in the Society for Maternal-Fetal

Medicine (SFMF) guidelines were included in the study. Accordingly, fetal growth restriction was defined as the estimated fetal weight (EFW) or abdominal circumference (AC) in the ultrasonographic evaluation below the 10th percentile for gestational age. Cases with FGR criteria at and after 32 weeks of gestation were accepted as LO-FGR (11). Gestational age was confirmed using first-trimester ultrasound findings or the date of the last regular menstrual period.

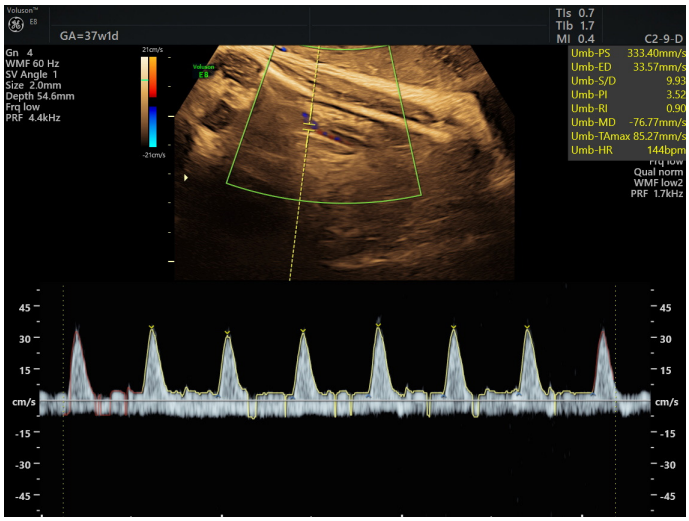
Ultrasonography

Sonographic evaluations of all participants were performed using the Voluson E8 ultrasound device (GE Healthcare, Milwaukee, WI) with a 3.5-MHz convex transducer (6C1-PVT-375BT) transabdominal probe. Fetal biometric measurements were undertaken by measuring head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL). EFW and percentile ratios were calculated according to the formula of Hadlock et al. (12). In all fetuses, Doppler examinations of the UA, MCA, uterine artery (UtA), and FA were undertaken. The cerebroplacental ratio (CPR) was obtained by dividing the pulsatility index (PI) of the MCA by the pulsatility index of the UA (MCA PI / UA-PI). The cerebroplacental-uterine ratio (CPUR) was determined as the ratio of the CPR measurement to the UtA PI (13). The measurements of the FA were made by performing Doppler ultrasonography on the lower extremity, where the femoral bone closest to the ultrasound probe was clearly visualized. The angle between the transducer and the bone was set to 45° or less (Figure 1). All other ultrasonographic Doppler measurements were undertaken by an experienced sonographer in accordance with standard recommendations.

Statistical Analysis

SPSS version 22 (IBM, Chicago, IL, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was used to determine whether the data complied with a normal distribution. After it was determined that the data did not conform to a normal distribution, the Mann-Whitney U test was conducted for the comparison between the two groups. The chi-square test was used when examining categorical variables. $p<0.05$ was considered statistically significant.

Figure I. This Doppler image shows the technique of measuring blood flow of the femoral artery in the fetal lower extremity, where the femoral bone is clearly visible. The measurement was taken at 37+1 weeks.



Results

The study included 168 pregnancies, of which 83 presented with LO-FGR and 85 were healthy controls. (Table I) shows the demographic data and ultrasonography parameters of all participants. Age, BMI, gravida, parity, and gestational week were similar between the two groups. Among the ultrasound parameters, the UtA PI, systolic/diastolic ratio (S/D) of the UA, peak systolic volume (PSV) of the MCA, and multiples of median (MoM) of the MCA PSV were also similar. However, the LO-FGR group had significantly lower MCA PI and FA PI values ($p<0.001$ and $p=0.002$, respectively) and a statistically higher UA PI measurement ($p=0.048$). In addition, CPR and CPUR were statistically significantly lower in the LO-FGR group ($p<0.001$ and $p=0.018$, respectively).

The 83 cases with LO-FGR in the study group were further divided into two groups according to the NICU requirements. While 15 newborns were admitted to NICU, 68 did not require intensive care. The ultrasonography parameters and perinatal

outcomes of the patients according to the NICU requirements are given in (Table II). The UA Doppler, UtA Doppler, MCA Doppler, and FA PI measurements were similar between these two groups. However, EFW, birth week, and birth weight were significantly lower in the NICU group (*p=0.033*, *p=0.013*, and *p=0.006*, respectively). Lastly, the rate of cases with an Apgar score of <7 at the first minute was 46.7% in the NICU group and 7.4% in the group that did not require neonatal intensive care (*p<0.001*).

Table I. Comparison of the demographic data and ultrasound parameters of the groups.

	Late-onset FGR (n = 83)	Control (n = 85)	*p value*
Age (years)	27 (6)	28 (8.5)	*0.695*
BMI (kg/m^2)	27.5 (3.7)	27.5 (4)	*0.726*
Gravida	2 (2)	2 (2)	*0.560*
Parity	0 (1)	1 (1)	*0.864*
Abortion	0 (1)	0 (1)	*0.474*
Gestational week[a]	37 (2)	36 (2)	*0.263*
EFW (grams)	2281 (451)	2482 (695.5)	***<0.001***
Placental localization, n (%)			
Anterior	40 (48.2%)	41 (48.2%)	*0.996*
Posterior	43 (51.8%)	44 (51.8%)	
UtA PI	0.7 (0.4)	0.7 (0.4)	*0.153*
UA S/D	2.6 (0.6)	2.4 (0.6)	*0.063*
UA PI	1.0 (0.2)	0.9 (0.3)	***0.048***
MCA PSV	49 (15.8)	47 (15)	*0.633*
MCA PSV MoM	0.9 (0.3)	0.9 (0.3)	*0.829*
MCA PI	1.5 (0.6)	1.9 (0.8)	***<0.001***
FA PI	4.5 (1)	4.1 (1.3)	***0.002***
CPR	1.6 (0.7)	2.1 (1)	***<0.001***
CPUR	2.3 (1.8)	2.8 (2)	***0.018***

(FGR: fetal growth restriction, BMI: body mass index, kg: kilogram, m^2: square meters, EFW: estimated fetal weight, UtA: uterine artery, PI: pulcatility index, UA: umbilical artery, S/D: systole/diastole, MCA: middle cerebral artery, PSV: peak systolic velocity, MoM: multiples of median, FA: femoral artery, CPR: cerebroplacental ratio, CPUR: cerebroplacental-uterine ratio)

[a]Gestational week at which ultrasonographic evaluation was made.

Data presented as median (interquartile range) or count (percentage). *p<0.05* accepted as statistically significant.

Discussion

This prospective study evaluated the relationship between FA Doppler measurements and poor perinatal outcomes in pregnant women presenting with FGR. The results showed that the FA PI value was higher in the FGR cases than in the controls. We also found that the FA PI value was similar between those with and without the NICU requirement among the FGR cases.

There is no gold standard definition for FGR. In most studies, FGR is defined as the estimated fetal weight <10th percentile. In the Delphi consensus published in 2016, a differentiation was made between early- and late-onset FGR by taking 32 weeks of gestation at a cut-off value in the absence of congenital anomalies. For late-onset FGR, if AC/EFW is <3rd percentile or AC/EFW is <10th percentile, the UA PI or UtA PI is defined as >95th percentile or CPR <5th percentile (14).

Late-onset FGR (LO-FGR) represents 70–80% of all FGR cases (15). Studies have shown that UA can identify severe placental insufficiency but fails to detect mild cases of placental insufficiency in LO-FGR. In addition, LO-FGR has no natural history, and these patients can experience rapid worsening without ultrasonographic findings (16, 17). Other fetal vascular Doppler assessments, including those of the UtA and MCA, have been recommended since UA Doppler cannot provide definitive findings for the identification of LO-FGR cases (17).

Only a few studies have performed the Doppler examination of peripheral arteries in patients with FGR. Peripheral blood vessels of fetuses with FGR may be deficient in nutrients and oxygen (18). In a study that conducted the Doppler examination of the tibial artery in patients with LO-FGR, the findings obtained from this examination were reported to be associated with adverse perinatal outcomes, such as acidemia and respiratory requirements (19). The

first study on the Doppler examination of the FA in FGR cases was conducted in 1991, in which the FA PI measurement was observed to increase linearly as the gestational week of the cases progressed, and two fetuses with FGR had abnormal FA Doppler findings died after birth (20). Another study found that acute hypoxemia in healthy fetuses caused a sudden decrease in both fetal heart rate and blood flow to the FA (21). In a study evaluating 221 patients, a high resistance pattern was observed in FA Doppler examinations throughout pregnancy (22). Due to the brain-sparing effect in FGR cases, Doppler examinations of the extremities have also attracted the attention of researchers. In the current study, we also observed a higher FA PI measurement in the LO-FGR cases than in the controls. However, in the LO-FGR group, the FA Doppler measurements of the cases with and without the NICU requirement were similar; therefore, these measurements did not have any utility in predicting adverse perinatal outcomes in patients with FGR.

Many research initiatives have focused on establishing good diagnostic markers for FGR and predictive models for adverse outcomes in FGR based on Doppler ultrasound findings (23) Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clx00ED;nic and Hospital Sant Joan de Deu. The PORTO study suggested that functional parameters were required to predict poor perinatal outcomes in FGR (24). Although there is an association between abnormal MCA PI measurements and poor perinatal outcomes, it remains unclear whether preterm delivery provides any benefit. It has been reported that in 25% of LO-FGR cases, the MCA PI is <5th percentile, suggesting chronic hypoxia (16). On the other hand, a reduced PI in the MCA is also associated with poor perinatal outcomes and an increased risk of abnormal neurodevelopment (25). Similar to previous studies, we also determined the MCA PI to be lower in the LO-FGR cases compared to the controls. However, we did not observe any difference in the MCA PI between the cases with and without NICU requirements.

Table II. Comparison of demographic data, ultrasound parameters, and delivery outcomes according to NICU requirement among patients with late-onset FGR.

NICU requirement	NICU (n = 15)	No NICU (n = 68)	*p value*
Age (years)	28 (8)	27 (6)	*0.502*
BMI (kg/m^2)	27.6 (5)	27.4 (3.7)	*0.670*
Gravida	2 (1)	2 (2)	*0.421*
Parity	0 (1)	1 (1)	*0.208*
Abortion	0 (1)	0 (0.8)	*0.565*
Gestational week[a]	36 (3)	37 (2)	*0.115*
EFW (grams)	1918 (810)	2340 (427.8)	***0.033***
Placental localization, n (%)			*0.114*
Anterior	10 (66.7%)	30 (44.1%)	
Posterior	5 (33.3%)	38 (55.9%)	
UtA PI	0.7 (0.8)	0.7 (0.4)	*0.740*
UA S/D	2.5 (1.3)	2.6 (0.6)	*0.925*
UA PI	0.9 (0.4)	1 (0.2)	*0.772*
MCA PSV	49.9 (12.4)	49 (16.5)	*0.683*
MCA PSV MoM	0.9 (0.2)	0.9 (0.3)	*0.329*
MCA PI	1.5 (0.6)	1.5 (0.6)	*0882*
FA PI	4.7 (1.3)	4.5 (1)	*0.356*
CPR	1.6 (1.3)	1.6 (0.6)	*0.934*
CPUR	2.5 (3.2)	2.3 (1.7)	*0.714*
Delivery week	37 (3)	38 (1)	***0.013***
Mode of delivery, n (%)			*0.458*
Cesarean section	11 (73.3%)	43 (63.2%)	
Vaginal delivery	4 (26.7%)	25 (36.8%)	
Birth weight (grams)	2200 (710)	2405 (472.5)	***0.006***
Apgar score <7 at the first minute	7 (46.7%)	5 (7.4%)	***<0.001***
Apgar score <7 at the fifth minute	1 (6.7%)	0 (0%)	*0.181*

(BMI: body mass index, kg: kilogram, m^2: square meters, EFW: estimated fetal weight, UtA: uterine artery, PI: pulcatility index, UA: umbilical artery, S/D: systole/diastole, MCA: middle cerebral artery, PSV: peak systolic velocity, MoM: multiples of median, FA: femoral artery, CPR: cerebroplacental ratio, CPUR: cerebroplacental-uterine ratio)

[a]Gestational week at which ultrasonographic evaluation was made.

Data presented as median (interquartile range) or count (percentage). *p<0.05* accepted as statistically significant.

CPR, defined as the ratio of the MCA PI measurement to the UA PI measurement, has been shown to be more sensitive to hypoxia than its individual components (26). CPR is important in the management of LO-FGR because it helps predict adverse perinatal outcomes (27). Twenty to twenty-five percent of LO-FGR cases have abnormal CPR values before birth and have a higher rate of adverse outcomes (28, 29). In the current study, CPR was significantly lower in the FGR group than in the control group. However, CPR did not significantly differ according to the NICU requirement among the LO-FGR cases.

CPUR, obtained by adding the UA PI to the CPR value, has been investigated in terms of its ability to predict adverse perinatal outcomes. In a study of 891 fetuses, the addition of the UA Doppler to the CPR parameter did not result in any predictive improvement (30). In another study, CPUR was found to detect more FGR cases than any other measured Doppler parameter (31). A study examining the prognostic effects of LO-FGR in 114 patients reported that CPUR was independently associated with adverse outcomes (32). In the current study, the CPUR value was lower in the LO-FGR group compared to the control group. However, we did not observe any differences between the LO-FGR subgroups in terms of the prognostic value of CPUR.

Another predictor of poor perinatal outcomes among LO-FGR cases is a very small EFW. Among fetuses below the 10th percentile, those with an EFW of <3rd percentile have a much higher risk of adverse perinatal outcomes, independent of their CPR and UtA Doppler values (15). A study conducted with pregnant women with LO-FGR found that adverse perinatal outcomes increased as birth weight decreased (32). In our cases of LO-FGR, newborns requiring NICU had a statistically lower EFW. Although Doppler parameters are normal, the success of EFW alone in showing adverse perinatal outcomes, especially in LO-FGR cases, seems to be effective.

The relatively small sample size and single-center design of the study can be counted among its limitations. Another limiting factor was that we did not include the long-term outcomes of the newborns. In addition, femoral artery Doppler measurements were not performed intermittently. The strength of the study is its prospective design. Multicenter studies with larger samples are needed.

Inconclusion, this study showed that the FA PI measurement was higher in the late-onset FGR cases than in the healthy controls. However, Doppler examination of the FA was not found to be effective in demonstrating adverse perinatal outcomes. There is a need for multicenter studies to demonstrate the importance of the FA Doppler examination in patients with FGR and determine its utility in the prediction of adverse perinatal outcomes.

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