How to Cite:
Elgarhy, I. M. T., El-Hamed Sedek, A. E.-M. A., & Abo-Rehab Ali, A.-R. A. (2022). Evaluation of fetal cerebral blood flow perfusion using power doppler ultrasound angiography (3D-PDA) in growth-restricted fetuses. *International Journal of Health Sciences*, *6*(S5), 7192–7206. https://doi.org/10.53730/ijhs.v6nS5.10281

Evaluation of fetal cerebral blood flow perfusion using power doppler ultrasound angiography (3D-PDA) in growth-restricted fetuses

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***Abstract*---**Background: Fetal growth restriction is a common complication of pregnancy and, in severe cases, is associated with elevated rates of perinatal mortality, neonatal morbidity, and poor neurodevelopmental outcomes. Aim of the work: The main purpose of our study was to explore the potential of 3D Power Doppler Angiography to evaluate the cerebral circulation in growth restricted fetuses in pregnant women. Patients and Methods: This was a prospective cohort study; the study including 100 patients were recruited in this study and divided in to two groups, group (A) High risk group including 50 pregnant patients with IUGR and hypertension of pregnancy and group (B) control group including 50 pregnant without risk factors, The study was conducted in Al Azhar university hospital. Results: The mother age in high risk group ranged from 23 to 38 years with mean ±SD= 30.24± 5.15 years while the in control group the mother age ranged from 22 to 38 years with mean ±SD= 29.74± 4.59 years with no statistical significant difference between the two groups. The gestational age in high risk group had mean ±SD= 36.94± 1.99 weeks while the in control group the mean gestational age was 37.34± 1.87 weeks with no statistical significant difference between the two groups. Conclusion: According to study results, 3D sonography and power Doppler angiography can be considered as new techniques offering to study additional vascular parameters of the fetal brain allowing for the evaluation of early non-invasive "brain sparing markers" in IUGR fetuses.

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 April 2022, Manuscript revised: 18 June 2022, Accepted for publication: 27 July 2022

***Keywords*---**Power Doppler Ultrasound Angiography, Growth-Restricted Fetuses, blood flow perfusion.

Introduction

The evaluation of fetal brain blood flow can be considered very important because deficits in the perfusion of this territory may lead to inadequate development of the central nervous system and even jeopardize fetal vitality *(Goetzinger et al., 2018).* Fetal intrauterine growth restriction (IUGR) associated with placental insufficiency can present well-recognized perinatal and long-term consequence *(Rossi et al., 2011).* IUGR is a major contributor to perinatal morbidity and mortality, affecting 4% to 8% of pregnancies *(Muniyar et al., 2017).* Although IUGR is suspected in all fetuses with an ultrasound-estimated weight below the 10th percentile, this definition alone is unable to differentiate those fetuses who are constitutionally small versus those with a pathologic condition *(Caradeux et al., 2019).*

In pathologic cases of growth restriction, fetuses have a preferential redistribution of blood flow to the brain as an adaptive response to preserve cerebral oxygenation in the presence of chronic hypoxia, known as the “brain-sparing” response *(Donofrio et al., 2014).* The current clinical standard used to assess the fetal brain circulation is 2-dimensional (2D) pulsed Doppler evaluation of the middle cerebral artery. This approach has both technical limitations and practical concerns, including its inability to accurately detect subtle changes in blood flow in small vessels and its assumption that redistribution of blood flow to all regions of the brain is symmetric *(Zhu et al., 2016).* With the advent of 3dimensional (3D) power Doppler techniques, it has been possible to actually quantify blood flow in fetal organs, including the kidney, liver, and placenta, by assessing both vascularization and flow indices *(Stevenson et al., 2015).*

Three typical indices of a volume of interest were calculated by this method: the vascularisation index (VI), flow index (FI) and vascularisation-FI (VFI). The feasibility and reproducibility of Doppler signal quantification by calculating VI, FI and VFI were found to be satisfactory in vitro and in vivo *(van Oostrom et al., 2003).* A significant decrease in placental VI, FI and VFI was observed in preeclamptic patients during the first trimester18 as well as the second and third trimesters *(Rehab and Marwa, 2018).*

Aim of the Work

The aim is to explore the potential of 3D Power Doppler Angiography to evaluate the cerebral circulation in growth restricted fetuses in pregnant women.

Patients and Methods

Study setting:

The study had been conducted at Obstetrics and Gynecology department at AL Azhar university hospital from April 2020 to April 2021

Type of study and study population:
Prospective study, The study include two groups, group (A) High risk group including 50 pregnant patients with IUGR and hypertension of pregnancy and group (B) control group including 50 pregnant patients weeks without risk factors e.g hypertension, IUGR, etc.

Inclusion Criteria:
Patients with pregnancy above 27 weeks with IUGR and hypertension of pregnancy.

Exclusion Criteria:
Pregnancies below 27 weeks with fetal malformations or chromosomal defects, or conceived after assisted reproduction.

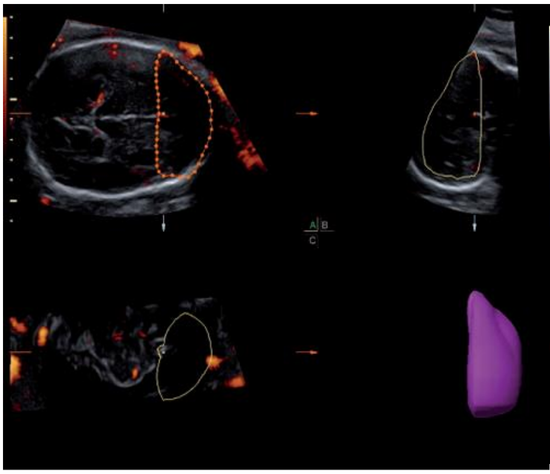
Operational design:
Explanation of the procedure to all women participating in the study, a written consent was taken from all patients before starting the study with counseling about risk and benefit of study.

Methods

All Patients were subjected to:
Complete history taking: Personal history including: name, Age, marital state, address, menstrual history: including age of Menarche, menstrual disturbance, dysmenorrhea, related symptoms, obstetric history including parity and mode of delivery, present history: of chronic diseases and medication, past history of HTN, family history of similar condition or diabetes, history of allergy to any medication, surgical history of operation, laparoscopic interference, treatment of hirsutism by Laser.

Examination

A. General examination: Evaluation of vital signs, measurement weight, height (BMI)
B. Abdominal and local clinical examination: to assess fundal level and gestational age, scar of previous operation, mass, tenderness or rigidity, any abdominal or pelvic clinically detectable pathology
C. Ultrasound examination.
D. Examination for any visible lesions or secretions
E. Power Doppler ultrasound angiography (3D-PDA)



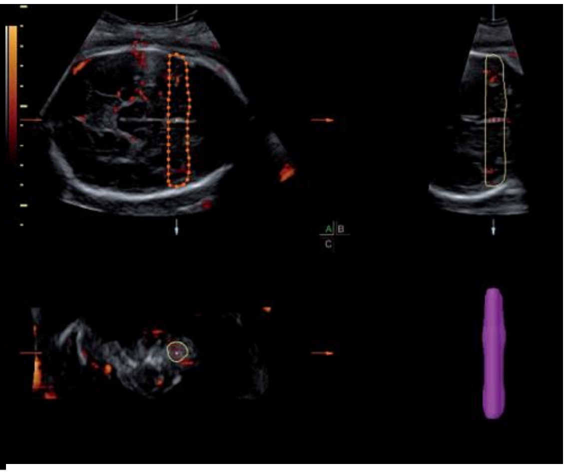


Fig 1: 3D-PDA of Zone 1 “Frontal Zone” Fig. 2: 3D-PDA of Zone 2 “Temporal Zone’

Statistical Analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(**Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance;., correlation by Pearson's correlation or Spearman's. P value was set at <0.05 for significant results & <0.001 for high significant result. Data were collected and submitted to statistical analysis. The following statistical tests and parameters were used.

Results

This prospective cohort Study was conducted at Obstetrics & Genecology Department, in AL Azhar university hospital. 100 patients were recruited in this study. The study including two groups, group (A) High risk group including 50 pregnant patients with IUGR and hypertension of pregnancy and group (B) control group including 50 pregnant patients without risk factors.

Table (1): Demographic & clinical characteristics among the two groups

		Group A (High risk group) (n = 50)		Group B (Control group) (n = 50)		Test value	P-value	Sig.
		n	%	n	%			
Age (years)	Mean± SD	30.24± 5.15		29.74± 4.59		0.504	0.614	NS
	Median	30		29.5				
	Range	23- 38		22- 38				
Residence	Urban	23	46.0%	24	48.0%	FET	1.00	NS

		Group A (High risk group) (n = 50)		Group B (Control group) (n = 50)		Test value	P-value	Sig.
		n	%	n	%			
	Rural	27	54.0%	26	52.0%			
Hypertension	Absent	26	52.0%	50	100.0%	31.579	**<0.001**	HS
	Present	24	48.0%	0	0.0%			
Gestational Age (weeks)	Mean± SD	36.94± 1.99		37.34± 1.87		1.021	0.307	NS
	Median	37		37.5				
	Range	27 - 40		27 - 40				
Mode of delivery	NVD	24	48.0%	27	54.0%	FET	0.689	NS
	CS	26	52.0%	23	46.0%			

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant,
SD= standard deviation, -comparison between groups done by Mann-Whitney test, Pearson Chi-Square test and Fischer- Exact test (FET)

Table (1) shows demographic & clinical characteristics among the two groups. The mother age in high risk group ranged from 23 to 38 years with mean ±SD= 30.24± 5.15 years while the in control group the mother age ranged from 22 to 38 years with mean ±SD= 29.74± 4.59 years with no statistical significant difference (p=0.614) between the two groups. Regarding residence, there was no statistical significant difference (p=1.00) between high risk group and control group. In high risk group women were hypertensive.

The gestational age in high risk group had mean ±SD= 36.94± 1.99 weeks while the in control group the mean gestational age was 37.34± 1.87 weeks with no statistical significant difference (p=0.307) between the two groups. Regarding mode of delivery, there was no statistical significant difference (p=0.689) between high risk group and control group.

Table (2): Laboratory data among the studied groups

		Group A (High risk group) (n = 50)		Group B (Control group) (n = 50)		Test value	P-value	Sig.
		n	%	n	%			
Hb level	Mean± SD	12.19± 0.68		11.81± 0.86		2.153	0.031	S
	Median	12.1		11.85				
	Range	10.90- 13.50		10.50- 13.10				
Platelets	Mean± SD	182.62 ± 27.21		204.26 ± 29.64		3.451	0.001	HS
	Median	180		202.5				
	Range	142.00- 231.00		152.00- 267.00				

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, *SD= standard deviation, -comparison between groups done by Mann-Whitney test*

Table 2 Regarding Hb level, there was statistically significant decrease in control group compared to high risk group (p= 0.031). There was statistically significant difference in platelets level between control group and high risk group (p= 0.001).

Table (3): Neonatal characteristics among the studied groups

		Group A (High risk group) (n = 50)		Group B (Control group) (n = 50)		Test value	P-value	Sig.
		n	%	n	%			
Birth Weight (grams)	Mean± SD	1921.16± 91.86		2773.74± 345.13		8.617	<0.001	HS
	Median	1912.50		2833.00				
	Range	1654.0 - 2104.0		2217.0 - 3325.0				
APGAR score (1 minute)	Mean± SD	7± 1		8± 1		5.172	<0.001	HS
	Median	7		8				
	Range	5- 9		7- 9				
APGAR score (5 minutes)	Mean± SD	8± 1		9± 1		4.579	<0.001	HS
	Median	8		9				
	Range	5- 10		8- 9				
NICU admission	No	42	84.0%	47	94.0%	2.554	0.110	NS
	Yes	8	16.0%	3	6.0%			

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant,
SD= standard deviation, -comparison between groups done by Mann-Whitney test, Pearson Chi-Square test.

Table (3) shows neonatal characteristics among the studied groups. It was noticed that birth weight was significantly decreased in high risk group compared to control group (p<0.001). Concerning APGAR score, the scores was significantly decreased in high risk group compared to control group after one & five minutes (p<0.001). 8 (16%) neonates in high risk group and 3 (6%) in control group needed NICU admission with no statistically significant difference between the both groups (p= 0.11).

Table (4): Three dimensional Power Doppler Angiography parameters values in Zone 1 in the studied groups

		Group A (High risk group) (n = 50)		Group B (Control group) (n = 50)		Test value	P-value	Sig.
		n	%	n	%			
Vascularity Index	Mean± SD	2.2± 0.2		2.3± 0.3		1.687	.092	NS

		Group A (High risk group) (n = 50)		Group B (Control group) (n = 50)		Test value	P-value	Sig.
		n	%	n	%			
	Median	2.2		2.3				
	Range	1.7 - 2.6		1.3 - 3.0				
Flow Index	Mean± SD	31.2± 2.5		31.9± 3.7		1.079	.281	NS
	Median	31.0		31.6				
	Range	25.9 - 35.7		22.4 - 42.3				
Vascular Flow Index	Mean± SD	0.8± 0.1		0.8± 0.1		0.349	.727	NS
	Median	0.8		0.8				
	Range	0.6- 0.9		0.4- 1.0				
Volume	Mean± SD	29.1± 2.9		33.3± 3.4		5.688	<0.001	HS
	Median	28.6		33.2				
	Range	24.2 - 38.1		26.4 - 41.0				

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant,
SD= standard deviation, -comparison between groups done by Mann-Whitney test

Table (4) shows the values of the vascular parameters (VI, FI and VFI) and the volume of the sampled brain in zone 1 for high risk and control groups. The volume was significantly decreased in high risk group compared to control group while there was no statistically significant difference between the both groups regarding VI, FI and VFI values (p= 0.092, 0.281 and 0.727 respectively).

Table (5): Three dimensional Power Doppler Angiography parameters values in Zone 2 in the studied groups

		Group A (High risk group) (n = 50)		Group B (Control group) (n = 50)		Test value	P-value	Sig.
		n	%	n	%			
Vascularity Index	Mean± SD	5.2± 0.9		3.4± 0.6		7.644	<0.001	HS
	Median	5.3		3.3				
	Range	2.8 – 8.1		2.3 – 4.9				
Flow Index	Mean± SD	34.4± 5.5		27.4± 3.3		6.236	<0.001	HS
	Median	35.2		27.6				
	Range	19.6 – 44.3		19.8 – 33.5				
Vascular Flow Index	Mean± SD	3.5± 0.2		1.2± 0.1		8.739	<0.001	HS
	Median	3.5		1.2				
	Range	2.9 – 3.9		1.1- 1.3				
Volume	Mean± SD	5.3± 0.8		5.0± 1.1		1.152	0.249	NS
	Median	5.2		5.1				
	Range	3.6 – 7.2		1.3 – 7.1				

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant,
SD= standard deviation, -comparison between groups done by Mann-Whitney test

Table (5) shows the values of the vascular parameters (VI, FI and VFI) and the volume of the sampled brain in zone 2 for high risk and control groups. The VI, FI and VFI values was significantly increased in high risk group compared to control group ($p<0.001$) while there was no statistically significant difference between the both groups regarding volume ($p= 0.249$).

Discussion

The evaluation of fetal brain blood flow can be considered very important because deficits in the perfusion of this territory may lead to inadequate development of the central nervous system and even jeopardize fetal vitality. Fetal intrauterine growth restriction (IUGR) associated with placental insufficiency can present well-recognized perinatal and long-term consequences. Some authors demonstrated that neurodevelopment dysfunction in IUGR infants involves general cognitive competence, suggesting dysfunction in the frontal lobe networking, limbic system and hippocampus and changes in the morphology of neural structures such as the retinal optical nerve *(Rossi et al., 2011).*

Fetal intrauterine growth restriction (IUGR) associated with placental insufficiency can present well-recognized perinatal and long-term consequences. Some authors demonstrated that neurodevelopment dysfunction in IUGR infants involves general cognitive competence, suggesting dysfunction in the frontal lobe networking, limbic system and hippocampus and changes in the morphology of neural structures such as the retinal optical nerve *(Voicu et al., 2020).* The presence of neurological damage originating in different brain areas is associated with an unpaired blood supply. The “brain sparing effect” (blood flow centralization process) can be considered as an adaptive response that preserves brain oxygen supply in the presence of chronic hypoxia. This process is identified clinically by a reduced Doppler pulsatility index (PI) in the middle cerebral artery (MCA). However, vasodilatation of the MCA might have a poor sensitivity to detect fetuses in the initial stages of increased brain perfusion *(Stefopoulou et al., 2021).*

Fetal growth restriction (FGR) is a common complication of pregnancy and, in severe cases, is associated with elevated rates of perinatal mortality, neonatal morbidity, and poor neurodevelopmental outcomes. The leading cause of FGR is placental insufficiency, with the placenta failing to adequately meet the increasing oxygen and nutritional needs of the growing fetus with advancing gestation. The resultant chronic fetal hypoxia induces a decrease in fetal growth, and a redistribution of blood flow preferentially to the brain. However, this adaptation does not ensure normal brain development *(Malhotra et al., 2017).*

Early detection of brain injury in FGR, allowing for the prediction of short- and long-term neurodevelopmental consequences, remains a significant challenge. Furthermore, in FGR infants the detection and diagnosis of neuropathology is complicated by preterm birth, the etiological heterogeneity of FGR, timing of onset of growth restriction, its severity, and coexisting complications *(Dall’Asta et al., 2021).*
Because the analysis of fetal brain circulation is of great interest when following up fetuses with growth restriction (FGR), 3D power Doppler studies may add valuable information to that obtained from 2D standardized Doppler evaluation.

Hemodynamic redistribution, which consists of blood flow redistribution toward essential fetal organs (brain, heart, and adrenal glands) at the expense of the other organ systems (lungs, kidneys, and bowel), represents one of the major fetal mechanisms to preserve vital organs, such as brain, from hypoxic damage. Currently this situation is normally diagnosed by using a combination of color and pulsed Doppler detecting decreased vascular impedance, usually caused by vasodilatation, at the middle cerebral artery *(Bartha et al., 2009).*

The main purpose of our study was to explore the potential of 3D Power Doppler Angiography to evaluate the cerebral circulation in growth restricted fetuses in hypertensive pregnant women. This was a prospective cohort study; the study including 100 patients were recruited in this study and divided in to two groups, group (A) High risk group including 50 pregnant patients with IUGR and hypertension of pregnancy and group (B) control group including 50 pregnant without risk factors, The study was conducted in AL Azhar university hospital.

In the present study, as regard demographic and clinical characteristics among the two groups; The mother age in high risk group ranged from 23 to 38 years with mean ±SD= 30.24± 5.15 years while the in control group the mother age ranged from 22 to 38 years with mean ±SD= 29.74± 4.59 years with no statistical significant difference (p=0.614) between the two groups. In high risk group, women were hypertensive, as regard the gestational age; in high risk group had mean ±SD= 36.94± 1.99 weeks while the in control group the mean gestational age was 37.34± 1.87 weeks with no statistical significant difference (p=0.307) between the two groups. Regarding mode of delivery, there was no statistical significant difference (p=0.689) between high risk group and control group.

In comparison with the study of *Rossi et al. (2011)* which conducted on a total of 105 pregnant women with a gestational age ranges from 34+0 to 36+0 weeks were included in the present study. The mean maternal age was 30.6±3.1; 43% of the women were primigravida and 57% was multigravida respectively; a total of 46% was primipara whereas 54% was multipara. In another study of *Addley et al. (2017)* reported that mean ±SD of age in normal group was 29.5 (7.0) and was 28.4(6.0) years in PE group, as regard the gestational age; in high risk group had mean ±SD= 34+0 weeks while the in control group the mean gestational age was 35+4 weeks, There was no statistically significant difference in age, body mass index or gestation between women with a normal pregnancy and women with preeclampsia.

On the other hand, as regard Hb level, there was statistically significant decrease in control group compared to high risk group (p= 0.031). There was statistically significant difference in platelets level between control group and high risk group (p= 0.001). This can be explained by that we recruited in our study hypertensive pregnant women who had lower platelets. High risk pregnancy refers to pregnancy accompanied by factors which increase the risk of neonatal mortality and morbidity. Based on statistics 10-20% of pregnancies are reported as high risk pregnancies. Neonatal state of health has a considerable effect on future health and life. Since neonate`s immune system and other organs in preterm neonate are not developed completely, they are at risk of many threats resulting neonatal admission in neonatal intensive care units (NICUs) for a short or long time in the first month of life *(Cömert et al., 2012).*

In the current study, neonatal characteristics among the studied groups were be assessed, It was noticed that birth weight was significantly decreased in high risk group compared to control group ($p<0.001$). Concerning APGAR score, the scores was significantly decreased in high risk group compared to control group after one & five minutes ($p<0.001$). 8 (16%) neonates in high risk group and 3 (6%) in control group needed NICU admission with no statistically significant difference between the both groups ($p= 0.11$).

In agreement with our findings, the study of *Saadat et al. (2007)* reported that the birth weight was statistically significantly lower in women with preeclampsia (high risk pregnancy) than in women with normal blood pressure ($p < 0.0001$). The percentage of women with low birth weight was also different between two groups (patient group, 32% vs. control group, 4.8%; $p < 0.0001$). The mean Apgar score in neonates at 1 and 5 minutes of the preeclamptic group were 7.6 and 8.8, respectively, which were lower than for neonates of healthy women (8.9 and 9.9 at 1 and 5 minutes, respectively). According to the results, only cesarean delivery was more frequent in preeclamptic women, and no significant differences in other variables between the two groups were seen. On the contrary, *Xiong and Fraser (2004)* found that there were no differences in mean birth weight between women with high risk pregnancy and women with normal blood pressure.

The standard technique used to assess fetal blood flow is usually the bi-dimensional Doppler. In contrast to this conventional method, which analyzes the frequency shift of blood velocity information, power Doppler sonography uses the amplitude component of the signals received to represent the number of moving blood cells *(Moron et al., 2010).* In fact power Doppler is useful in situations of low-velocity blood flow because it allows the detection of minimal alterations in blood flow. Moreover, power Doppler does not show aliasing effect and the colour map is independent of the insonation angle. The introduction of 3D power Doppler (3D-PD) and the vascularization histogram allowed quantifying the vascularization and blood flow to the placenta and several fetal organs. The use of 3D-PD is useful in the evaluation of fetal brain vessels because of their small caliber *(Sun et al., 2018).*

Power Doppler evaluates the amplitude of the received signals, indicating the number of moving cells, so this method is more sensitive for evaluating small vessels and low-velocity flows, allowing the detection of minimal changes in the blood flow. Such characteristic is extremely relevant in the evaluation of low-resistance vessels *(Oglat et al., 2018).* With the arrival of 3D ultrasonography, power Doppler started being utilized for 3D analysis of blood flow and vessels. However, the first studies with this new technique included only a qualitative evaluation by means of 3D reconstruction of the vascular structure of a region of interest (ROI), without quantifying the vascularization and the blood flow of this territory *(Altriagey et al., 2019).*

In the present study, Two regions of interest (ROI) were be defined within the fetal brain. Zone 1 is anterior to the cavum septi pellucidi (CSP). Zone 2 is defined by a rectangle obtained tracing a contour between the temporal bones as wide as the CSP, corresponding to the area of the middle cerebral artery. The Flow Index (FI), the Vascularization Index (VI), the Vascularization and Flow Index (VFI) were determined in both areas in both IUGR and AGA fetuses by a single operator, and we found that as regard three dimensional Power Doppler Angiography parameters values in Zone 1 in the studied groups; the volume was significantly decreased in high risk group compared to control group while there was no statistically significant difference between the both groups regarding VI, FI and VFI values ($p= 0.092$, 0.281 and 0.727 respectively).

While as regard the values of the vascular parameters (VI, FI and VFI) and the volume of the sampled brain in zone 2 for high risk and control groups; The VI, FI and VFI values was significantly increased in high risk group compared to control group ($p<0.001$) while there was no statistically significant difference between the both groups regarding volume ($p= 0.249$). In agreement with our findings, *Rossi et al. (2011)* reported that as regard vascular parameters (VI, FI, VFI) in Frontal Zone (zone 1) for the FGR group and the control group, VI and VFI were both increased in the FGR group with statistical significance comparing to control group ($P <0.05$), while the values of VI, FI, VFI in Temporal Zone (zone 2) for FGR group and control group revealed that VI and VFI were significantly decreased in the FGR group comparing to the control group.

Recently *Jones et al. (2009)* specified that an increased VI in the ROI can be due both to an increased dimension of a vessel (vasodilatation) and to diversion to other vessels secondary to pressure rise, showing a strong linear relationship to volume flow rates. The initial preferential increment in blood supply to the Frontal Zone can be associated with preservation of general cognitive functions such as impulse control, language, memory, problem solving and suggests a hierarchical order in the protection of brain functions *(Rovas et al., 2005).* With this in view, MCA vasodilatation (MCA PI reduction) may do not represent a protective response but rather the starting point after which the protection of the frontal area begins to decline. The real “brain sparing effect” seems to be marked by hemodynamic changes in the anterior cerebral artery (ACA) and consequently in its districts. If confirmed, these findings might have important implications, especially since Doppler findings may be subtle and accurate identification of growth restriction arising in the third trimester still provides a challenge. The clinical significance of the observations reported in the present study remains to be established by larger prospective studies with long term postnatal neurological follow-up *(Rossi et al., 2011).*

Hernandez-Andrade et al. (2008) reported that the Vascularity Index (VI) and Vascular Flow Index (VFI) obtained by three-dimensional Power Doppler Angiography of the frontal zone of the fetal brain (zone 1), sprinkled mainly by the anterior cerebral artery, demonstrate the “frontal brain sparing effect” in fetuses with IUGR presenting with normal Doppler flow indices of umbilical and middle cerebral arteries. On the other hand, these vascular parameters were decreased in zone 2, suggesting a vascular redistribution during brain sparing effect according to a regional increase in bloody supply to the frontal region. This shift may indicate that in very early stages of IUGR general cognitive functions, such as impulse control, language, memory, problem solving and socialization may be preferentially preserved suggesting a hierarchical order in the protection of the brain functions.

Moreover, *Addley et al. (2017)* reported that indices of fetal cerebral perfusion were not different between women with a normal pregnancy in comparison to women with pre-eclampsia (Table 2). The mean (SD) for FI, VI and VFI was not different between groups. For FI, the mean (SD) was 22.4 (5.7) vs. 21.1 (4.3) for normal vs pre-eclampsia groups respectively (p=0.49). For VI, the mean (SD) was 64.7 (40.4) vs. 79.1 (27.4) respectively; p = 0.28. For VFI, the mean (SD) was 14.8 (10.3) vs. 16.1 (5.5) respectively; p= 0.66.

Dubiel et al. (2005) evaluated 3D power Doppler angiography by using a different technique and a different index (mean signal intensity) and suggested that hemodynamic redistribution appeared physiologically at the end of pregnancy. This finding was not compared with the results obtained with the use of the conventional 2D Doppler indices. It is known that MCA PI and peak systolic velocity decreases and increases, respectively, with gestation suggesting this phenomenon. In spite they studied a group of high-risk pregnancies, no specific group of fetuses with FGR and/or placental insufficiency was studied. Again, the use of the sphere standardized technique and several 3D indices may be the best method to evaluate and analyze the results of the 3D power Doppler studies.

Assessment of the fetal cerebral circulation is particularly useful to observe hemodynamic changes associated with chronic hypoxia and the severity of FGR. The gold standard for fetal brain hemodynamic evaluation is middle cerebral artery (MCA) flow and pulsatility index *(- et al., 2016).* Reduced pulsatility index in the MCA demonstrates cerebral vasodilatation (and brain-sparing), and a number of studies show that MCA vasodilatation predicts neurodevelopmental deficits after birth *(Figueras et al., 2011).*

All available data to date indicate that vasodilation of the MCA reflects an advanced and severe stage of growth restriction and brain injury, with high risk for abnormal neurodevelopment *(Rossi et al., 2011).* The anterior and posterior cerebral arteries might also provide cerebral hemodynamic insight, characteristic of the onset and the degree of brain-sparing *(Hernandez-Andrade et al., 2012).*
Our findings are in line with recent study of *Figueroa-Diesel et al. (2007)* in growth-restricted fetuses suggesting that the anterior cerebral artery shows Doppler signs of vasodilatation before these are observed in the MCA. Indeed, in this study, the observation of an abnormally reduced PI in the MCA was concurrent with the onset of a progressive reduction in blood perfusion to the frontal area. These data might suggest that, contrary to current beliefs, an abnormal MCA might actually indicate the starting point after which the hemodynamic protection of the frontal area starts to decline. The strengths of this study are that the 3D ultrasound technique was robustly standardized and the two groups of patients were matched for general characteristics.

Finally, according to the results we obtained in this study, 3D sonography and power Doppler angiography can be considered as new techniques offering additional vascular parameters allowing for detection of early non-invasive “brain sparing markers” in fetuses affected by FGR, even without any pathological 2D

Doppler velocimetry. Construction of reference charts and inter-observer variability study of 3D-PDA vascular indexes of fetal brain circulation in normal pregnancies need to be planned.

In conclusion, According to these results, 3D sonography and power Doppler angiography can be considered as new techniques offering to study additional vascular parameters of the fetal brain allowing for the evaluation of early non-invasive “brain sparing markers” in IUGR fetuses. Fetal cerebral 3D power Doppler indices can be easily and reliably used during pregnancy and may be more sensitive than MCA measurements to detect fetuses at risk of hypoxia and, therefore brain injury, but further studies are needed to set up the clinical value of this new technology.

Conclusion

According to study results, 3D sonography and power Doppler angiography can be considered as new techniques offering to study additional vascular parameters of the fetal brain allowing for the evaluation of early non-invasive “brain sparing markers” in IUGR fetuses. Fetal cerebral 3D power Doppler indices can be easily and reliably used during pregnancy and may be more sensitive than MCA measurements to detect fetuses at risk of hypoxia and, therefore brain injury, but further studies are needed to set up the clinical value of this new technology.

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