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Prediction of fetal hypoxia by ductus venosus Doppler pattern in high-risk pregnancies

Obstetrics & Gynecology

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ABSTRACT

Background: Ductus venosus doppler has effective role in treatment of disorders that put the fetus at risk of cardiovascular diseases. In antenatal assessment, Doppler ultrasonography is increasingly being used to evaluate the blood flow volume rate in vessels during the cardiac cycle in the fetoplacental, uteroplacental circulation.

Aim of the work: To discover if ductus venosus Doppler velocimetry may give earlier prediction of fetal hypoxemia than umbilical and middle cerebral artery blood doppler velocity in high-risk pregnancy or not.

Patients and methods: According to the inclusion criteria, 60 pregnant women after the age of fetal viability (28 weeks of pregnancy) were included in the study. In order to facilitate statistical description, we divided the cases into 2 groups (Hypoxic and Non-Hypoxic groups), according to Apgar score, if less than 7 at 5 minutes or Cord PH less than 7.35.

Results: The best cut-off value for the ductus venosus RI was >0.45 with a sensitivity of 98.7%, specificity of 56.7%, positive predictive value (PPV) of 80%, and negative predictive value (NPV) of 100%. When comparing the diagnostic ability of ductus venosus RI and middle cerebral artery systolic/diastolic ratio, the ductus venosus resistance index showed the highest diagnostic ability 91% against 71% for the middle cerebral artery systolic/diastolic ratio.

Conclusion: Ductus venosus Doppler US is a useful way to assess fetoplacental circulation and has a good ability to predict fetal low oxygen. The most reliable index to predict low oxygen is the resistance index.

Keywords: *Fetal hypoxia; Ductus venosus; Doppler.*

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INTRODUCTION

The ductus venosus is a vascular shunt that connects the umbilical vein to the inferior vena cava within the fetal liver parenchyma. The ductus venosus provides oxygenated blood and nutrient-rich venous blood to follow from the placenta to the myocardium and brain.[1]

The ductus venosus has a central role in the distribution of highly oxygenated umbilical venous blood to the heart. Its waveform is related to the pressure-volume changes in the heart atria. Therefore, it is important the monitoring any fetal condition that may affect forward cardiac function. [2]

Moreover, in fetal growth restriction, the ductus venosus plays an important role in circulatory adaptation to hypoxia, but the ways are yet unknown. Under hypoxic conditions, increased blood shunting through the ductus venosus has been observed in both animal and human studies.[3]

Fetal hypoxia is a condition in which the fetus's growth is hampered by a lack of oxygen, which raises the danger of perinatal and infant death. It accounts for 23% of all newborn fatalities worldwide.[4]

Doppler flowmetry is a good way for the prediction of intrauterine growth retardation in high-risk pregnancies.[5] Use of Doppler ultrasound in high-risk pregnancies reduces the risk of perinatal death, serial monitoring of Doppler changes in ductus venosus may be beneficial.[6]

Doppler US has been used to amount blood flow velocity in vessels during the heart cycle in the fetoplacental & uteroplacental circulations, with an

attention on arteries for the measurement of the cardiac output (COP) downstream distribution.[7]

The present study aimed to find out if ductus venosus Doppler velocimetry might give an earlier anticipate of fetal hypoxemia than umbilical and MCA blood Doppler velocity in high-danger pregnancy or not.

PATIENTS AND METHODS

The current study was a prospective research that was carried out at Sayed Galal university Hospital. The study included 60 high-risk, pregnant women, after the age of fetal viability (≥ 28 weeks of gestation) attending outpatient clinics (optics) or admitted to Obstetrics and Gynecology department in the period from December 2018 to December 2021 upon the following criteria.

And to facilitate the description of the case census, they were divided into two groups according to Apgar score.

Inclusion criteria: Normal anatomy in a singleton fetus, and as well as one or more of the prerequisites below;(small for gestational age fetus, oligohydramnios, placental vascular disorders as evidenced by a local reference's abnormal umbilical artery pulsatility index ranges, and HTN with pregnancy).

Exclusion criteria: Fetus with major congenital malformation as indicated by ultrasound examination, multiple gestations, and a patient who is planned for urgent termination.

All of the 60 cases were subjected at the first visit to the following:

Personal history; Surname, birthdate, marital status, parity, profession, address, a set of medically significant habits, the current pregnancy's history; focused on the risk factors associated with pregnancy as well as recognition of the inclusion and exclusion criteria, menstrual history, obstetric history, previous medical history, and family medical history.

Examination as follows; general examination, abdominal examination, auscultation of fetal heart rate, and ultrasound study done every two weeks till the time of termination.

Doppler examination: Flow velocity waveforms of the umbilical artery, middle cerebral artery, and ductus venosus were recorded during foetal quiescence. The resistance index (RI), pulsatility index (PI), and mean systolic/diastolic ratio (S/D) of sequential flow velocity waveforms were calculated. The US beam and the direction of blood flow were constantly at a 30 degree angle. The Doppler analysis was carried out. Doppler indices had been calculated by the dedicated software supplied within the Doppler device. The mean value of consecutive waveforms had been assessed.

Time of delivery; emergent termination for cases of abnormal ductus venosus Doppler as severe preeclampsia or absent or reversed end-diastolic blood flow. Elective termination for other cases under control.

The newborn was subjected to Apgar scoring after 1 and 5 minutes by a neonatologist attending delivery. All cases are followed up on until they are discharged.

Statistical analysis:

Results of the present study were statistically analyzed using SPSS 25 (IBM, USA). Findings were represented as Mean ± SD or number and percentage. Numerical data were compared using Fisher exact test, Chi-square test, and unpaired student t-test as appropriate. sensitiveness and specificity of the various venous parameters of DV, MCA, and UA in the prediction of low PH were calculated and receiver operating characteristic curves were calculated for each finding. If the P-value is less than 0.05, the result is significant; otherwise, it is non-significant.

RESULTS

The research comprised the following: 60 high-dangers, pregnant women, after the age of fetal viability (≥ 28 weeks of gestation). To facilitate statistical description, we divided the cases into 2 categories (Hypoxic and Non-Hypoxic groups), according to Apgar score, if less than 7 at 5 minutes or Cord PH less than 7.35 (Acidosis).

Ultrasound fetal measurements and Doppler ultrasound were performed and 21 cases were found with abnormal Ductus venosus pattern flow shapes A, B, C and after labor neonatal admission to the neonatal intensive care unit due to hypoxia was recorded.

Age of patient (Years)	Group Ⅰ (hypoxic) (n= 35)		Group Ⅱ (non-hypoxic) (n= 25)		Total (n= 60)		P
	No.	%	No.	%	No.	%	
20 – 30	15	43	15	60	30	50	0.1
31 – 40	20	57	10	40	30	50	
Mean ± SD	31 ± 6. 26		29 ± 5. 87		30 ± 6. 15		
Range	21 – 40		20 – 40		20 – 40		
Median (IQR)	32 (24 - 36)		29 (23 - 33)		31 (24 - 35)		

Table 1: Comparison between the studied groups as regards the age of the patient (Years).

As regards the age of the studied sample, in group I 15 patients were between the age of 20 & 30 years (43%), & 20 patients (57%) were between 31 and 40 years of age and group II 15 patients (60%) were between 20 and 30 years of age and 10 patients (40%) were between 31 and 40 years of age**.** The data presented previously is not significant. (p= 0.1) (Table 1)**.**

Blood pressure (mmHg)	Group Ⅰ (hypoxic) (n= 35)		Group Ⅱ (non-hypoxic) (n= 25)		Total (n= 60)		P
	No.	%	No.	%	No.	%	
Systolic							
120-139 mmHg	8	23	2	8	10	17	0.003
140-159 mmHg	19	54	23	92	42	70	
≥ 160 mmHg	8	23	0	0	8	13	
Mean ± SD	140 ± 11.83		139.5 ± 11.54		140 ± 11.83		
Range	120 – 160		120 – 159		120 – 160		
Median (IQR)	140 (120 - 160)		139.5 (120 - 159)		140 (120 - 160)		
Diastolic							
60–89 mmHg	8	23	2	8	10	17	0.001
90-109 mmHg	19	54	23	92	42	70	
≥ 110 mmHg	8	23	0	0	8	13	
Mean ± SD	85 ± 14.71		84.5 ± 14.4		85 ± 14.71		
Range	60 – 110		60 – 109		60 – 110		
Median (IQR)	85(60- 110)		84.5 (60- 109)		85(60 - 110)		

Table 2: Comparison between the studied groups as regards the blood pressure (mmHg).

The SBP, in group I 8 patients (23%) had normal systolic blood pressure (120 – 139 mmHg), 19 patients (50%) had hypertensive SBP (140-159 mmHg); which (diagnosed as 15 patients had gestational HTN and 4 patients had mild preeclampsia) and 8 patients (23%) had severe preeclampsia ≥ 160 mmHg and group II 2 patients (8%) had normal SBP (120 – 139 mmHg, and 23 patients (92%) had hypertensive SBP (140-159 mmHg); which (diagnosed as 20 patients had gestational hypertension and 3 patients had mild preeclampsia). As regards the DBP, in group I 8 patients (23%) had a diastolic blood pressure between (60 - 89 mmHg), 19 patients (54%) had a DBP of (90 -109 mmHg); which (diagnosed as 15 cases had gestational HTN and 4 patients had mild preeclampsia) and 8 patients (23%) had a diastolic blood pressure ≥ 110 mmHg and in group II 2 patients (8%) had a diastolic blood pressure between 60 and 89 mmHg, 23 patient (92%) had a diastolic blood pressure of (90-109 mmHg); which (diagnosed as 20 patients had gestational hypertension and 3 patients had mild preeclampsia).The previously shown data differed significantly between group I & group II as regards both systolic and diastolic blood pressure (p= 0.003; 0.001, respectively) (Table 2).

Cord blood PH	Group Ⅰ (hypoxic) (n= 35)		Group Ⅱ (non-hypoxic) (n= 25)		Total (n= 60)		P
	No.	%	No.	%	No.	%	
< 7.25	21	60	0	0	21	35	0.001
7.25 - 7.35	14	40	0	0	14	23	
> 7.35	0	0	25	100	25	42	
Mean ± SD	7.23 ± 0.08		7.37 ± 0.06		7.29 ± 0.10		
Range	7.10 - 7.35		7.35 - 7.47		7.10 - 7.47		
Median (IQR)	7.23 (7.17 - 7.30)		7.36 (7.35 - 7.41)		7.30 (7.21 - 7.35)		

Table 3: Comparison between the studied groups as regards the cord blood PH.

As regards the cord blood PH, a group I had 21 patients (60%) had a PH < 7.25, 14 (40%) had a PH between 7.25 and 7.35**.** Group II had 25 patients (100%) had a PH level of > 7.35**.**These data differed at a highly- level that is statistically important (p= 0.001) (Table 3)**.**

Danger factors	Group Ⅰ (hypoxic) (n= 35)		Group Ⅱ (non-hypoxic) (n= 25)		Total (n= 60)		X2	P
	No.	%	No.	%	No.	%		
Gestational Hypertension	15	43	20	80	35	58	11.1	0.0007
Mild Preeclampsia	4	11	3	12	11	11	0.006	0.9
Severe Preeclampsia	8	23	0	0	8	13	8.013	0.004
Oligohydramnios	5	14	2	8	7	12	0.526	0.4
Intra-Uterine Growth Restriction	3	9	0	0	3	5	2.212	0.13

Table 4: Comparison between the studied groups as risk factors.

As regards gestational HTN, group Ⅰ had 15 patients (43%), while group Ⅱ had 20 patients (80%); the total sample had 35 patients with gestational hypertension (58%). These data show a highly statistically significant difference (p= 0.007) **.** As regards mild preeclampsia, group Ⅰ had 4 patients (11%) and group Ⅱ had 3 patients (12%), while the total sample had 7 patients with mild preeclampsia (12%). As regards the severe preeclampsia, group Ⅰ had 8 patients (23%), while group Ⅱ didn't have any patients with severe preeclampsia, the total sample had only the patients of group Ⅰ with severe preeclampsia (8 patients; 13%). These data are highly statistically significant (p= 0. 004) **.** As regards the oligohydramnios, group Ⅰ had 5 patients (14%), while group Ⅱ had 2 patients (8%), and the total sample had 7 patients (12%). As regards the intra-uterine growth restriction, only 3 patients in group Ⅰ (9%) and in the total sample (5%) had IUGR (Table 4)**.**

		AUC (%)	SE	P	95% Cl
UA	pulsatility index	0. 63	0. 056	0. 27	0. 53-0. 72
	resistance index	0. 53	0. 0634	0. 16	0. 43-0. 63
	systolic/diastolic ratio	0. 51	0. 06	0. 8	0. 41-0. 61
MCA	pulsatility index	0. 65	0. 055	0. 72	0. 55-0. 74
	resistance index	0. 77	0. 058	0. 01	0. 58-0. 87
	systolic/diastolic ratio	0. 82	0. 052	0. 005	0. 68-0. 95
DV	pulsatility index	0. 84	0. 18	0. 03	0. 88-0. 93
	resistance index	0. 95	0. 06	0. 0008	0. 91-1. 03
	systolic/diastolic ratio	0. 73	0. 8	0. 63	0. 63-0. 80

Table 5: ROC curve to know the best cutoff for MCA, UA & DV PI, RI, & S/D to detect low oxygen.

Umbilical artery pulsatility index was not reliable to predict hypoxia (AUC 63%), resistance index was also not reliable (AUC 53%), and in addition, S/D was not dependable to anticipate low oxygen (AUC 51%) (p= 0.27, 0.16, 0.8; respectively). The MCA pulsatility index was not reliable to predict hypoxia (AUC 63%), the resistance index was weak to predict hypoxia (AUC 77%), and in addition, S/D was reliable to predict hypoxia (AUC 82%). The best cut off value for the middle cerebral artery S/D was ≤4.66 with a sensitivity 88.8%, specificity 57.9%, positive predictive value (PPV) of 71%, and negative predictive value (NPV) of 79% with a diagnostic accuracy of 71% positive likely-hood ratio (+LR) = 2.30 negative likely-hood ratio (-LR) = 0.056. As regards ductus venosus, the most reliable index to predict hypoxia is the resistance index (AUC 95%; p= 0.0008, highly significant), moreover, the PI showed to be reliable to predict hypoxia as well (AUC 84%; p= 0.03, significant), however, systolic/diastolic ratio was not reliable to anticipate low oxygen. The best cut off value for the ductus venosus RI was >0.45 with a sensitivity of 98.7%, specificity 56.7%, positive predictive value 80% and negative predictive value 100% with a diagnostic accuracy of 91% positive likely-hood ratio (+LR) = 3.19 negative likely-hood ratio (-LR) = 0. When comparing the diagnostic ability of ductus venosus RI The ductus venosus resistance index outperformed MCA systolic/diastolic ratio by 91 percent, compared to 71 percent for MCA S/D ratio. (Table 5 and Figs. 1, 2).

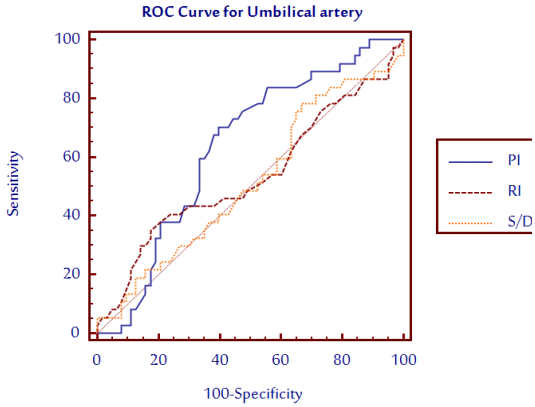

Fig. 1: ROC Curve for the umbilical artery.

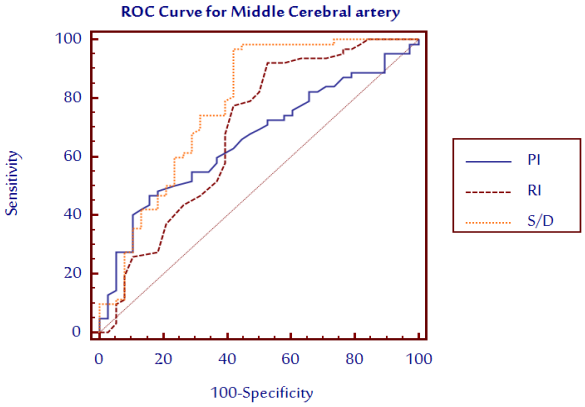

Fig. 2: ROC Curve for middle cerebral artery.

Shape	Group I (hypoxic) (n= 35)		Group II (non-hypoxic) (n= 25)		Total (n= 60)		X^2	P
	No.	%	No.	%	No.	%		
Normal	14	40	25	100	39	65	36.4	0.0001
A	5	14	0	0	5	8	4.562	0.03
B	9	26	0	0	9	15	10.831	0.001
C	7	20	0	0	7	12	8.013	0.004

Table 6: Comparison between the studied groups as regards the Ductus Venosus Doppler pattern flow.

Normal shape waves in ductus venosus Doppler accounted for 14 patients in group I (40%) and all patients in group II (100%). Shape A accounted for 5 patients in group I (14%). Shape B accounted for 9 patients in group I (26%). Shape C accounted for 7 patients in group I (21%). All of the previously reported data were statistically highly significant (p= 0.0001; p= 0.03; p= 0.001; p= 0.004, respectively (Table 6).

DISCUSSION

In this study the mean age of placenta previa patients (study group) was 32.0 ± 3.3 years while that of upper segment implanted placenta (control group) was 30.3 ± 4.0 years. Moreover the number of previous cesarean sections in the study group was 2.9 ± 1.0 CS, while the control group was 2.5 ± 0.6 CS. While the mean number of parity for the study group was 3.3 ± 1.0 and that of the control group 2.8 ± 0.9.

Also, the mean age of the adherent placenta previa was 31.9 ± 3.7 while the mean age of non-adherent placenta previa was 32.0 ± 3.1. Which showed no significance between the two groups. Also the parity

between two groups showed no significance. However the mean number of CS in the adherent placenta previa was 3.2 ± 1.0 while the mean number of previous CS in the non-adherent placenta previa was 2.5 ± 0.7 which shows significant between both groups, which proves that previous CS is a risk factor for adherent placenta.

Assessment of placenta intra-operatively among the group with placenta previa showed 30 (60 %) patients with adherent placentas and 20 (40 %) patients with non-adherent placentas. On the other hand none of the patients of the control group showed adherent placenta, which proves that placenta previa is the main risk factor for adherent placenta.

The final pathological analysis of the 30 patients with adherent placenta revealed 20 cases of placenta accreta, 5 cases of placenta increta and 5 cases of placenta percreta. All of these patients underwent CS hysterectomy. The 5 patients with placenta percreta, the placenta invaded the bladder and had primary bladder repair during the operation.

In 20 of the 50 patients, the conclusive diagnosis of placenta previa without accreta was made. Due to uncontrollable bleeding from the implantation site following placental separation, two of these patients underwent caesarean hysterectomy.

The mean value of MS-AFP of the cases of placenta previa was 139.0 ± 74.4 IU/ml where abnormal elevations (>2.5 MoM) were found in 40 out of the 50 patients with mean gestational age of 36.9 ± 0.8 weeks while the control group showed mean value of 41.9 ± 19.2 ng/ml where only two of the patients showed abnormal elevations, with mean gestational age of 37.2 ± 0.6 weeks with high significance.

On analyzing MS-AFP within the placenta previa patients we found out that the mean value of MS-AFP of cases of adherent placenta previa was 170.4 ± 70.6 IU/ml were abnormal elevations (>2.5 MoM) were found in 27 out of the 30 patients of placenta accreta, with sensitivity of 88.9 %, while the mean value of MS-AFP of cases of non adherent placenta previa was 56.2 ± 39.4 IU/ml were 13 out of the 20 patients showed abnormal elevations (>2.5 MoM) with a low specificity of 33.3 % but with high significance.

So we could conclude that placenta previa is associated with higher levels MS-AFP than patients with upper segment implanted placenta, and patients with placenta accreta are associated with even higher elevations of MS-AFP with high sensitivity but with low specificity.The mean value of MS-AFP according to the type of placenta accreta was 179.3 ± 67.1 IU/ml for placenta accreta, 127.3 ± 82.6 IU/ml for placenta increta and 177.7 ± 86.4 IU/ml for placenta percreta, which showed no significance between the 3 groups.Bahadue et al.[11] found a link between higher MS-AFP levels and a higher risk of persisting placenta previa, which is similar to our findings. A MSAFP score of less than 1 MoM is linked to a lower probability of previa persistence until birth.

Furthermore, Zelop et al.[12] discovered elevated MS-AFP levels (between 2.3 and 5.5 MoMs) in 45 percent of 11 women with placenta accreta, whereas none of the controls with placenta previa without accreta did. Although these studies are small, they suggest that women with elevated MSAFP levels with no other obvious cause should be considered at increased risk of placenta accreta.It's also been suggested that in women with placenta accreta, abnormalities in the placental-uterine interface cause foetal alpha-fetoprotein to seep into the maternal blood, resulting in higher MS-AFP levels. [12]

Similarly, Belfort et al.[13] found that increased maternal blood alpha-fetoprotein has been linked to placenta accreta, and that there is a clear link between the amount of invasion and the elevation of this analyte. Similarly, Mosbeh et al.[14] discovered that a maternal blood alpha-fetoprotein level of >2.5 MoM is linked to placenta accreta. In addition, Matsuzaki et al.[15] showed that 9 of the 20 (45 percent) women with placenta accreta had increased MS-AFP levels (between 2.7 and 40.3 multiples of the median [MoM]), whereas the controls all had MS-AFP levels within normal limits (less than 2.0 MoM).

Regarding ultrasonographic diagnosis, when we compared greyscale ultrasound to 3D Doppler in the diagnosis of placenta accreta within patients with placenta previa.Intraoperative 30 (60 %) of patients in the study group showed placenta accreta while 20 (40 %) of the patients did not show placenta accrete.With greyscale ultrasound 23 patients (77.8%) showed at least one criterion for placenta accreta, while 7 patients did not show evidence of placenta accrete for the 30 patient confirmed intraoperative as accreta. While with 3D power Doppler 20 patients (66.7%) showed at least one criterion for placenta accreta, while 10 patients did not show evidence of placenta accrete for the 30 patient confirmed intraoperative as accreta.

Comparing the results of the greyscale ultrasound to the definitive diagnosis intraoperative we find that, greyscale ultrasound successfully diagnosed 23 out of the 30 cases of placenta accreta and failed to diagnose the remaining 7 cases with sensitivity of 77.8 %. Also, greyscale ultrasound successfully diagnosed non-adherent placenta in 13 out of the 20 patients and showed criteria of adherence in the 7 remaining patients with specificity of 66.7 %. Positive predictive value 77.8 % and negative predictive value of 66.7 % with high significance (p value 0.02).

Also, on comparing 3D power Doppler results to intraoperative diagnosis, 3D power Doppler successfully diagnosed 20 patients and failed to diagnose 10 patients with sensitivity of 66.7 %. In addition 3D ultrasound ruled out the diagnosis of placenta accreta in 10 patients and had false positives in 3 patients with specificity of 83.3 % and positive predictive value of 85.7 % and negative predictive value of 62.5 % with high significance (p value 0.01).

According to our study, greyscale ultrasound had a higher sensitivity of 77.8 % and negative predictive

value of 66.7 %, while 3D ultrasound showed higher specificity of 83.3 % and higher positive predictive value of 85.7 %. Also the addition of 2D ultrasound to 3D power Doppler will have higher sensitivity of 83.3 % and lower specificity of 66.7 %.

Compared to our study, Fukushima et al.[16] The presence of myometrial thickness less than 1 mm or huge placental lakes has been reported as a symptom of accretion of the placenta When both findings are present, they have a substantial positive predictive value (72 percent). According to Mittal et al.[17], the most relevant prognostic indicators were disruption of the placental-uterine wall interface and the presence of arteries traversing this site. Using a composite grading approach that included six sonographic observations, these researchers found 89 percent sensitivity and 98 percent specificity. The presence of "many coherent vessels in the basal view" has a 97 percent sensitivity, 92 percent specificity, and 76 percent positive predictive value on 3-dimensional power Doppler, according to a recent study. However, the number of people with placenta accreta who participated in these trials was limited, and there is no consensus on which characteristics are most useful in diagnosing placenta accreta. . Also sonographic detection of these criteria remain user dependent which require experience in the field remain the main drawback of ultrasound diagnosis.Finally, when the three groups were compared, MS-AFP was shown to be the most sensitive, with a sensitivity of 88.9%, followed by greyscale ultrasonography with a sensitivity of 77.8% and 3D power Doppler with a sensitivity of 66.7 percent. However, with a specificity of 33.3 percent, MS-AFP was the least specific, followed by greyscale ultrasonography with a specificity of 66.7 percent. , and 3D power Doppler with a specificity of 83.3 percent.

CONCLUSION

The findings revealed that ductus venosus resistance index is the most reliable index to give earlier prediction of fetal hypoxemia in high-risk pregnancy in comparison with umbilical artery and middle cerebral artery doppler.

Conflict of interest : none

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