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Correlation between fetal ductus venosus doppler velocimetry, pulsitility index (MCA/UA ratio) and amniotic fluid index in prediction Of perinatal outcome in preeclamptic pregnancies

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AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

SUMMARY

Background: Preeclampsia is considered a major obstetric problem with increased maternal and perinatal morbidity and mortality. The aim of this study was to evaluate the role of fetal Doppler in predicting adverse outcomes in Preeclamptic patients.

Methods: A prospective cross section study was conducted in two private hospitals among 96 women classified into 2 groups; 48 preeclamptic patients and 48 normotensive matched patients group. Ductus Venosus Doppler velocimetry pulsatility index, Middle Cerebral Artery/Umbilical Artery ratio, and amniotic fluid index were measured.

Results: All doppler indices were significantly higher in the Preeclampsia group in comparison to the control group ($p < 0.05$). all Doppler indices were significantly correlated with all neonatal adverse outcomes ($p < 0.05$).

Conclusion: In severe Preeclampsia, Doppler measurements remain the preferential indicator for adverse birth outcomes

Keywords: Severe preeclampsia; Adverse outcomes; Fetal Doppler indices; Ductus venosus

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INTRODUCTION

Preeclampsia (PE) is a complex pregnancy related hypertensive disorder arising after 20 weeks of gestation [1]. It represents a major health problem associated with substantial maternal and perinatal morbidity and mortality with high risk of long-term health consequences [2].

The relevance of PE worldwide ranges from 3 to 10% of all pregnancies with level of 70.000 or more maternal mortalities and over 500.000 fetal and neonatal deaths annually [1, 3].

According to the onset, PE is further subdivided into two main types, early onset preeclampsia (EOP) and late onset preeclampsia (LOP) with cut-point of ≤ 34 weeks gestation. LOP accounts for the majority of cases (> 80%) [4]. The pathogenesis of preeclampsia is quite complex and poorly understood. However, the main feature appeared is utero-placental insufficiency with compensatory changes of fetal circulation in response to hypoxia [4,5]. These circulatory changes could be detected non-invasively by Doppler ultrasound waveforms [5].

Therefore we evaluated middle cerebral artery (MCA) and the umbilical artery (UA) with ductus venosus by using different Doppler ultrasound parameters to measure its efficacy in predicting adverse outcomes in women with severe preeclamptic features presented at ≥ 34 weeks of pregnancy.

AIM OF THE STUDY

The aim of this work was to find a correlation between different fetal doppler parameters; Ductus Venosus Doppler velocimetry pulsatility index, (MCA/UA ratio) in to detect its diagnostic efficacy for predicting Preterm, NICU admission and neonatal Death in pre-eclamptic women.

PATIENTS AND PROCEDURES

Design: This study is a cross-sectional study and included 48 females with a singleton pregnancy suffering from severe preeclampsia and 48 normal females with a singleton pregnancy. Their age of gestation ranged between 34 weeks and 38 weeks. The study was performed in 2 private hospitals in Saudi Arabia, the study was approved

by the ethical committee of participated hospitals, all patients received informed consent after explanation of purpose and procedure of study. The study was conducted in the period of january 2020 till September 2020. The sample size was obtained to yield a 95% confidence level, 5% margin of error with anticipated response rate 80%.

Patients: All pregnant women who presented to Delivery unit at participated hospitals during a nine-month period were screened for eligibility. Preeclamptic group (Group I) was comprised of 48 women with a viable singlet pregnancy ≥ 34 weeks, complicated by severe PET. All women who met eligibility criteria and had existing medical disorder (e.g., diabetes, renal disorders, etc.), and those who were complicated by intrauterine fetal death and fetal anomalies were also excluded. A comparison group of 48 healthy, maternal parity-matched, gestational age-matched and age- matched women with uncomplicated pregnancies were recruited during the same period (Group II) (**Fig. 1.**).

Preeclampsia was diagnosed based on criteria set by International Society for the Study of Hypertension in Pregnancy (ISSHP) [6,7].

Method: To minimize interpersonal biases and assure consistency, all contributing physicians were instructed regarding inclusion and exclusion criteria, definitions and procedures before the study. In addition, the neonatologists evaluated the neonates in the delivery room for adequate Apgar score interpretation.

All women were subjected to the following;

- Complete history regarding demographic data (age, parity, and gestational age), current health status and presence of any chronic illnesses
- Clinical evaluation to detect signs of pre-eclampsia (Two well-trained nurses were assigned to evaluate the blood pressure for all study population using automated well-calibrated machine validated to be used in pregnancy following guidelines for blood pressure measuring in the clinic setting. Mercury sphygmomanometer was used concurrently according to National Institute for Health and Care Excellence (NICE) antenatal Care guidance steps [8].
- CBC, Coagulation profile, LFT and KFT.
- Ultrasound examinations were performed to detect amount of liquor, fetal weight and growth, Fetal Growth Restriction (FGR) was defined as an estimated fetal weight less than the 10th percentile or decreased fetal growth on serial ultrasound, Exclusion of congenital anomalies, NST was performed for all cases.

The Doppler measurements studied was as follow of the umbilical artery Pulsatility index rate (PI), the middle cerebral artery Pulsatility index rate (PI), the Ductus Venosus Pulsatility Index for Veins (PIV).

Doppler analysis was performed for all patients using well equipped ultrasound machine and by expert sonographers. Doppler indices of fetal UA, MCA and ductus Venosus were measured including:

Pulsatility index = Peak systolic velocity – End diastolic velocity / Time-averaged maximum velocity

Resistance index (RI) = systolic velocity—diastolic velocity / Peak systolic velocity

In the present study, reference values for Doppler indices were based on the study of Ciobanu et al. [7]. All measured Doppler indices were plotted on the appropriate reference range for appropriate same centile charts [7]. Umbilical artery, MCA and ductus venosus indices were defined as being abnormal if values > 95th percentiles, < 5th percentiles and >95th respectively.

Primary outcomes:

Assessing the association between the STUDIED Doppler indices and the adverse neonatal outcome.

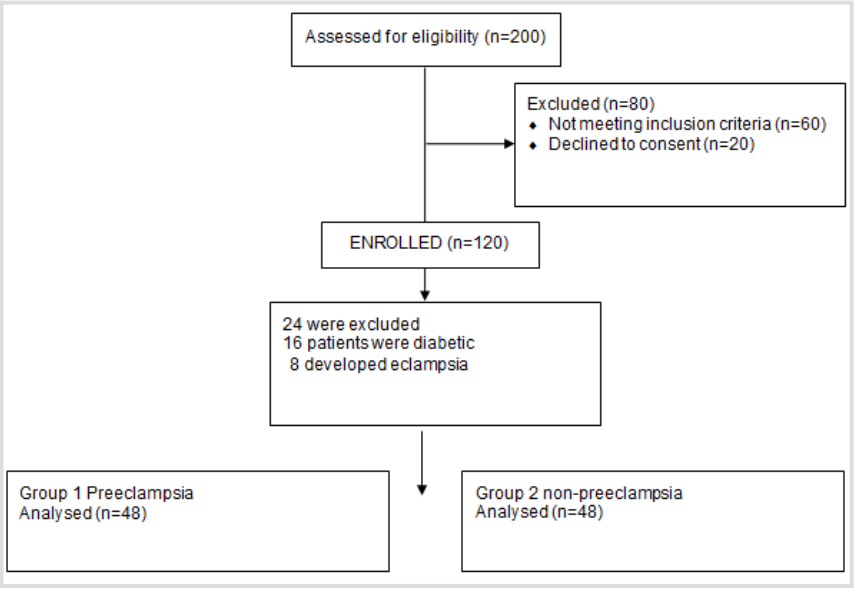

Fig. 1. Recruitment Flow Diagram.

Immediate pregnancy outcomes obtained were: the gestational age at delivery, mode and onset of labor and neonatal Apgar score at 1 and 5 minutes, neonatal PH, birth weight and need for NICU admission

STATISTICAL ANALYSIS

Numerical data will be explored for normality by checking the data distribution and using normality's tests (Kolmogorov-Smirnov and Shapiro-Wilk tests). Data will be presented as mean, standard deviation (SD).

Student's t-test will be used for parametric data to compare between the two groups.

Chi-square (x^2) test of significance was used in to compare proportions between qualitative parameters. The significance level will be set at $P \leq 0.05$. Statistical analysis will be performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

RESULTS

In total, 200 pregnant women with a mean age of 28.35±3.05 years were assessed for eligibility during the study period. Out of those patients, 60 participants didn't meet inclusion criteria and 20 didn't consent to be in the study. The recruitment pathway led to final participation of 96 patients allocated into two groups of 48, preeclampsia (Group I) and non-preeclampsia (Group II).

- There were no statistically significant differences in demographic data between the groups studied (**Tab.2**).
- The Preeclamptic group had significantly higher IUGR rates and other negative neonatal outcomes (**Tab.3.**).
- The Preeclamptic group had a significantly lower mean cord blood pH than the non-Preeclamptic group (**Tab.4.**).
- The APGAR score was significantly lower in the Preeclamptic group than in the non - Preeclamptic group (**Tab. 5.**).
- Ductus Venosus PI had a significant negative correlation with cord blood pH, AFI, APGAR at 1 minute and APGAR at 5 minutes, AFI correlated positively with cord blood pH, APGAR at 1 minute and APGAR at 5 minute and weight.) (**Tab. 6.**).
- The Ductus Venosus had a sensitivity of 75% and a specificity of 88.2%, it showed to have potential for use as a method of fetal assessment for preeclamptic pregnancy, Sensitivity and Specificity of pH regard IUGR was 75% and 89.8% respectively while Sensitivity and Specificity for AFI regard IUGR was 81.3% and 96.3% respectively (**Tab. 7.**) (**Fig. 2.**).

Tab. 1. Diagnostic criteria of pre-eclampsia and severe pre-eclampsia.

Preeclampsia
Elevated blood pressure (systolic ≥ 140 mm Hg, diastolic ≥ 90 mm Hg) Proteinuria of ≥ 0.3 mg in a 24-h urine collection specimen, protein /creatinine (mg/dl) ratio ≥ 0.3, or a urine dipstick protein of +1
Other maternal organ affection, including: Acute renal injury ;(creatinine ≥ 90 µmol/L; 1 mg/dL. liver impairment (ALT or AST > 40 IU/L) with or without right upper quadrant pain or abdominal (epigastric pain) Neurological complications e.g., headache, blurring of vision Hematological abnormalities (thrombocytopenia – platelet < 150,000/µL DIC, hemolysis) fetal affection intrauterine growth restriction
Severe features of preeclampsia Increased blood pressure (systolic ≥ 160 mm Hg, diastolic ≥ 110 mm Hg) Creatinine level (> 1.1 mg per dL [97 µmol per L] or ≥ 2 times over baseline) Hepatic impairment (ALT, AST levels ≥ 2 times upper limit of normal) or right upper quadrant pain or abdominal epigastric pain Blindness, stroke Platelet count < 100 × 103 per µL (100 × 109 per L) Pulmonary edema

Tab. 2. Obstetric history, Age, SBP and DBP distribution among studied groups.

Demographic Data	preeclampsia Group *(N=48)*	Non-preeclampsia Group *(N=48)*	Total (n=96)	Test value	p-value
Age (years)	28.46±3.48	28.25±2.59	28.35±3.05	t:0.333	0.740
Gravidity					
Multigravida	44 (91.7%)	45 (93.8%	89 (92.7%	x^2:0.154	0.695
PG	4 (8.3%)	3 (6.2%)	7 (7.3%)		
Parity					
P0	6 (12.5%)	4 (8.3%)	10 (10.4%)	x^2:1.506	0.471
P1-2	41 (85.4%)	44 (91.7%)	85 (88.5%)		
P>2	1 (2.1%)	0 (0.0%)	1 (1.04%)		
GA at delivery (wks.)	37.56±1.75	38.02±1.78	37.79±1.77	t:1.272	0.206
SBP (mmHg)	153.85±4.37	117.10±4.03	135.48±18.94	t:42.811	<0.001**
DBP (mmHg)	100.54±5.61	72.02±3.85	86.28±15.11	t:29.034	<0.001**
Using: t-Independent Sample t-test; x^2: Chi-square test; p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS					

Tab. 3. Intra uterine growth retardation distribution between groups and other fetal outcome parameters.

	preeclampsia Group *(N=48)*	Non-preeclampsia Group *(N=48)*	Total (n=96)	Test value	p-value
IUGR	16 (33.3%) NICU [11/16]	0 (0.0%) NICU [0]	16 (16.7%) NICU [11/16]	x^2:19.200 x^2:16.622	<0.001** <0.001**
Preterm	12 (25.0%) NICU [7/12]	10 (20.8%) NICU [4/10]	22 (22.9%) NICU [11/22]	x^2:0.236 x^2:0.697	0.627 0.404
Death	2 (4.2%)	0 (0.0%)	2 (2.1%)	x^2:2.043	0.153
Using: t-Independent Sample t-test; x^2: Chi-square test; p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS					

Tab. 4. Comparison between 2 groups regarding Doppler, cord blood PH and AFI.

	preeclampsia Group *(N=48)*	Non-preeclampsia Group *(N=48)*	Total (n=96)	Test value	p-value
DVPI	1.12±0.13	0.91±0.11	1.02±0.16	t:8.859	<0.001**
UARI	1.06±0.13	0.89±0.06	0.98±0.13	t:8.692	<0.001**
MCARI	0.62±0.06	0.61±0.03	0.61±0.05	t:1.214	0.228
Cord blood PH	7.14±0.04	7.19±0.03	7.16±0.05	t: -6.437	<0.001**
AFI	8.15±2.80	16.55±1.87	12.35±4.84	t: -17.272	<0.001**
Using: t-Independent Sample t-test; x^2: Chi-square test; p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS					

Tab. 5. Comparison between 2 groups regard neonatal outcomes.

	preeclampsia Group *(N=48)*	Non-preeclampsia Group *(N=48)*	Total (n=96)	Test value	p-value
APGAR at one minute	5.13±1.36	6.98±0.84	6.05±1.46	t: -8.032	<0.001**
APGAR at five minutes	7.08±1.51	8.81±0.87	7.95±1.50	t: -6.869	<0.001**
Baby Weight	1986.5±372.6	2877.3±239.7	2431.9±545.5	t: -13.931	<0.001**
Total NICU	18 (37.5%)	4 (8.3%)	22 (22.9%)	x^2:11.558	<0.001**
Using: t-Independent Sample t-test; x^2: Chi-square test; p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS					

Tab. 6. Correlation between DVPI and AFI with different parameters.

Parameters		DVPI	AFI
Cord blood PH	R	-0.972	0.866
	P	<0.001**	<0.001**
AFI	R	-0.930	--
	P	<0.001**	--
APGAR at one minute	R	-0.317	0.900
	P	0.036*	<0.001**
APGAR at five minutes	R	-0.298	0.863
	P	0.039*	<0.001**
Weight	R	-0.108	0.880
	P	0.237	<0.001**
Using: t-Independent Sample t-test; x^2: Chi-square test; p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS			

Tab. 7. Sensitivity and Specificity for DVI, PH and AFI cutoffs regard IUGR.

Test Result Variable(s)	AUC	Cut off	P	95% Confidence Interval		Sensitivity	Specificity
				Lower	Upper		
DVPI	0.783	>1.16	0.002*	0.687	0.861	75%	88.2%
Cord blood PH	0.795	≤7.11	<0.001**	0.701	0.871	75%	89.8%
AFI	0.855	≤6.11	<0.001**	0.768	0.918	81.3%	96.3%
AUC: Area under the curve; *p-value <0.05 is significant; **p-value <0.001 is highly significant							

DISCUSSION

Doppler flow ultrasound has been considered as a non-invasive tool for fetal surveillance in high-risk pregnancies and prediction of the adverse pregnancy outcomes [5]. Consistent with previous studies, using Doppler indices for comparison between preeclamptic pregnant patients and those with healthy pregnant females showed significant abnormalities in all Doppler parameters [9,10].

Serial Doppler measurements of fetal vessels mainly umbilical artery, middle cerebral artery and ductus venosus are used for monitoring high risk pregnancies. The majority of the severely growth restricted fetuses have pathological venous velocimetry, most significant an increased pulsatility in the ductus venosus which is a sign of impaired fetal myocardial function [11].

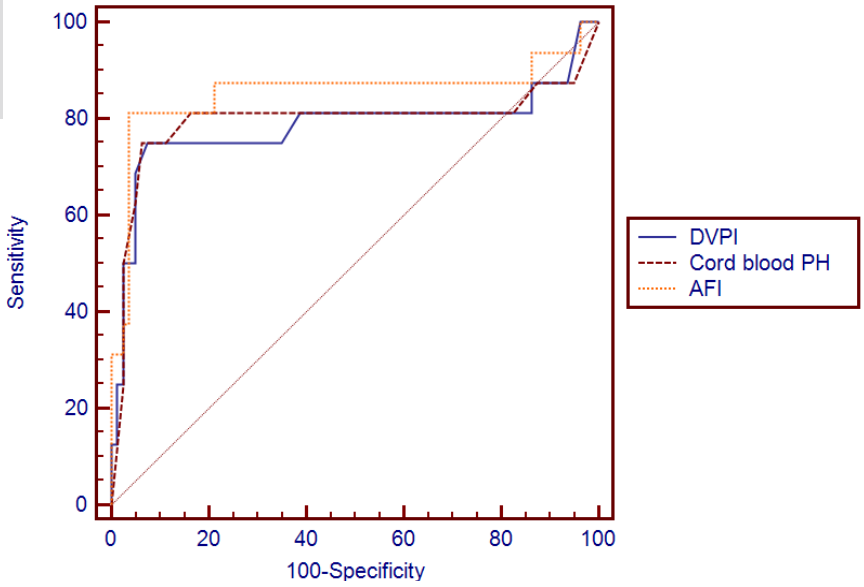

Fig. 2. Receiver-operating characteristic (ROC) curve for prediction of IUGR using the DVPI, Cord blood pH and AFI.

The Results of the present study and their Interpretation

The present study show no statistically significant difference between preeclamptic group and non-hypertensive group as non-hypertensive were selected as age-matched, parity- matched and gestational aged matched.

In the preeclamptic group 16 patients developed IUGR with no patients in non-hypertensive group (high statistically significant difference P<0.001), from those 16 patients 11 neonate have entered NICU. The second cause of NICU admission was prematurity which were 12 cases in group of preeclampsia and 10 cases in non-hypertensive group and this was expected as the selection of the patients was gestational aged matched selection. There was a high statistically significant difference between 2 groups as regarding total NICU admission (P<0.001).

The results of the present study showed that there was significant increase in resistance index in umbilical artery, significant lower MCA RI and significant increase in DVPI in preeclamptic group in comparison to non-hypertensive group. This is explained by the state of generalized vasoconstriction and hypoxia that occur in preeclampsia. The AFI is significant lower in preeclamptic group as fetal renal blood flow decreases to spare blood for important organs as brain. Fetal adverse outcomes as IUGR, preterm, NICU, fetal death were all significantly higher in Preeclampsia reflecting the severity of this disease and its great affection of fetus. Severe placental insufficiency occurring in preeclampsia leads to decrease in fetal blood flow and causes a step-wise increase in growth restriction. In Preeclampsia, raised Umbilical artery RI is used as a marker for decreased placental blood flow caused by local hypoxia resulting in the increase of peripheral vascular resistance and placental insufficiency The neonatal parameters were also affected in the form of significant decrease in cord PH reflection the state of acidemia that resulted from Hypoxia same for APGAR at 1 and 5 minutes

In the present study the Ductus Venosus PI had a significant negative correlation with cord blood pH, AFI, APGAR at 1 minute and APGAR at 5 minutes, AFI correlated positively with cord blood pH, APGAR at 1 minute and APGAR at 5 minute and weight.) The Ductus Venosus had a sensitivity of 88 % and a specificity of 73.5 %, it showed to have potential for use as a method of fetal assessment for preeclamptic pregnancy, Sensitivity and Specificity of pH regard IUGR was 80.0% and 83.3% respectively while Sensitivity and Specificity for AFI regard IUGR was 72% and 96% respectively.

Comparison of the results of current study in relation to similar studies

The results of current study demonstrated higher significant difference in preeclamptic group as regard adverse perinatal outcome of IUGR, Preterm delivery and higher NICU admission. This is in line of study Elsayed et al [12], they studied the effect of PET on 50 patients and the prediction of same doppler parameters that we used in our study. They found that the ability of an abnormal Ductus Venosus Doppler index was 32% to predict adverse perinatal outcomes [12]. Both Hecher et al., and Rizzo et al., [13,14] reported that fetal acidosis correlated significantly with elevated venous Doppler indices in both the Ductus venosus and inferior vena cava.

Baschat et al. [15] reported a lower birth weight in cases of abnormal ductus venosus flow. This was in agreement with the present study where the frequency of IUGR was highest in cases with abnormal venous flow. In addition, the mean birth weight in the group of abnormal ductus venosus flow was significantly lower than those of the group of non-hypertensive group with normal blood flow (p 0.001) [15].

Similarly, this study reported a significantly lower mean cord blood pH in the group of abnormal ductus venosus flow (preeclamptic group) than in the control group. This is in accordance with results of El Sayed et al. [12]

In the study of Mari et al. [16], they found that in non-preeclamptic pregnancies, Doppler measurements can predict fetal outcome. However, in pre-eclamptic patients, the vascular changes can change dramatically in few hours from a state with normal Umbilical Artery (UA) diastole and normal Ductus Venosus (DV) flow to a state of UA reversed flow and DV reversed flow [16].

Bilardo and Baschat [17] in their study on preterm severe IUGR population, they reported that the likelihood of IUFD and stillbirth increase with the degree of affection in venous Doppler. Ominous Venous Doppler findings are the absent or reversed flow in the ductus venous. In their study a 25% stillbirth rate in a, these Doppler findings had a 65% predictive sensitivity and 95% specificity [17].

RECOMMENDATIONS FOR FUTURE STUDIES

Further studies are needed with large number of patients to determine the normal local reference charts for fetal Doppler indices especially the fetal ductus venosus to predict adverse fetal and neonatal outcomes in preeclampsia.

CONCLUSION

The results here are re-confirmation of one the preceding knowledge, however, we believe that area/ institute –specific data is important for the practice.

ETHICS APPROVAL

Study approved by appropriate ethical Committee.

CONSENT FOR PUBLICATION

Non-applicable.

AVAILABILITY AND DATA MATERIAL

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors report there are no competing interests to declare.

FUNDING

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