Research Article

Correlation Between Fetal Ductus Venosus Doppler and Amniotic Fluid Index in Prediction of Perinatal Outcome in Preeclamptic Pregnancies

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Abstract
Objective: To find correlation between fetal Ductus Venosus Doppler and Amniotic fluid index in prediction of perinatal outcome in preeclampsia. **Methods**: Fifty pregnant women were admitted in the high risk pregnancy unite (HRPU) in obstetrics and gynecology department of zagazig university hospital, during the period from, March 2018 to January 2019. **Results**: This study included 50 females with a singleton pregnancy suffering from severe preeclampsia and normal 50 females with a singleton pregnancy. Their gestational age ranged between 32 weeks and 40 weeks gestation. **Conclusion**: Doppler of the UA remains the most extensively investigated tool. There is less evidence available for the use of DV Dopplers and AFI . Current RCOG guidance recommends the use of these Dopplers in the surveillance and timing of delivery. DV Doppler is the most recent technique for the monitoring fetal cardiac circulation and predicting neonatal outcome.
Keywords; Preeclamptic Fetal Ductus Venosus Doppler, Amniotic Fluid Index, Prediction, Perinatal Outcome, Pregnancies
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Introduction
Hypertensive disorders complicating pregnancy are common and form one of the deadly triad along with haemorrhage and infection that results in much of the maternal morbidity and mortality related to pregnancy[1].

Preeclampsia is acute specific hypertension due to pregnancy (one of PIH) Occurring only in human female during pregnancy. Characterized by hypertension with proteinuria and/or edema in the second half of pregnancy (except with vesicular mole) or early puerperum [2], mortality related to pregnancy[2].

The main pathologic feature of preeclampsia is vasospasm, which leads to impairment of blood flow to various organs particularly the uterus and placenta[3]. Impairment of uteroplacental circulation affects the placental functions that sustain the fetus. Preeclampsia is conventionally considered to be a maternal disorder in which the fetus is an incidental participant. A more complete perception is that the placental problem causes both maternal fetal syndromes[4,5].

Antenatal prediction and identification of the fetuses at risk for preventable morbidity and mortality can help in improvement of outcome for the mother and her baby in most cases. The past decade has seen an increasing interest in Doppler ultrasound as it provides non invasive access to uteroplacental and fetal circulation and therefore might yield direct information on pathophysiology of vascular insufficiency[6]. This measurement is considered to be a useful adjunct in the management of pregnancies complicated by fetal-growth restriction[7,8].

The ductus venosus is the primary shunt regulating nutrient flow to the liver and heart (Kessler et al., 2011).(9) It acts as the first partition that determines the proportion of this nutrient rich blood that continues directly toward the heart. Its trumpet shape and narrow diameter are the main factors that produce a marked blood flow acceleration of umbilical venous blood toward the heart. (Baschat, 2011)[10]. Ductus Venosus provides a unique combination of advantages: It is a primary regulation of venous return in both normal and

abnormal fetus, it is a direct conduit of right atrial retrograde pulse wave and it is readily imaged because of its very focal high velocity color Doppler signal and characteristic audio signal from 12 to 40 weeks (Baschat et al., 2003)[11].

Doppler ultrasonography and Biophysical Profile Scoring (BPS) are the principal surveillance tools in pregnancies complicated by placental vascular insufficiency and fetal growth restriction (IUGR). These antenatal testing modalities aim to detect fetal compromise by evaluating fetal manifestations of altered oxygenation and metabolic status (Ferrazzi et al., 2002).[12].

Amniotic fluid plays a major role in the normal growth of the fetus, promotes muscular-skeletal development, allows for easier fetal movement and protects it against injuries (Shivalingaiah et al., 2015)(13) there are several ways to assess quantity of amniotic fluid as vertical pocket, but amniotic fluid index (AFI) by four quadrant technique is most popular and reliable method of quantifying amniotic fluid till today. The assessment of amniotic fluid volume is very crucial for the survival of the fetus (Nardozza et al., 2012).(13)

Materials and Methods

Fifty pregnant women were admitted in the high risk pregnancy unite (HRPU) in obstetrics and gynecology department of zagazig university hospital, during the period from, March 2018 to January 2019.

Patients:

This study included 50 females with a singleton pregnancy suffering from severe preeclampsia and normal 50 females with a singleton pregnancy. Their gestational age ranged between 32 weeks and 40 weeks gestation.

Inclusion criteria

- Age: 18 – 40 years.
- Gestational age > 34 weeks.
- Singleton pregnancy.
- Systolyic blood pressure ≥160mmHg
- Diastolic blood pressure ≥110 mm
- Proteinuria on catheterized urine specimen of at least 2+ on dipstick .
- No obstetric or medical complications of pregnancy apart from preeclampsia

Exclusion criteria

- Multiple pregnancies.
- Preterm pregnancies.
- Fetal abnormalities or aneuploidy.
- Antepartum still birth.
- Pregnant females with other medical disorders (Diabetes Mellitus, history of having cardiac, liver or renal disease).

II. Plan of the study:

All the patients included in the study were subjected to the following:

1. A verbal informed consent.
2. Full history taking: personal, menstrual, obstetrical, past and family history with special consideration to history of PIH.
3. Thorough clinical examination including:
   - General examination: including vital signs, chest, heart, abdominal and lower limb examination.
   - Full obstetric examination.
4. Blood pressure measurement:
   - In semi-sitting position.
   - Using appropriate cuff size.
   - Patient's arm supported and positioned at level of the heart. Listen for a muffling sound (Korotkoff's sounds phase 5).
   - Using mercury sphygmomanometer.
5. Ultrasound assessment:

To confirm dating, liquor Volume, placental separation and assess fetal wellbeing (Gestational age, EFBW, Biophysical profile, Ductus Venosus Doppler). The biophysical profile (BPP) consists of 2 parts, a Non-Stress Test (NST) and an ultrasound evaluation. Five specific fetal attributes are studied and "scored" during the BPP: Breathing, Movement, Muscle Tone, Heart Rate and Amniotic Fluid.

Technique of Ultrasonography:

1. Each eligible patient was examined by transabdominal ultrasound with convex transducer (Using Samsung Medison Sono Ace R5 machine equipped with the C2-8 Curved array transducer with 51mm foot-print and set at a frequency of 3.5MHz) at Zagazig University.
2. During ultrasound examination, the routine ultrasound examination of the fetus at this age, (including fetal biometry, confirmation of growth patterns, EFBW, normal fetal situs, assessment of the amniotic fluid, excluding any abnormalities in the placental

site or shape excluding any fetal congenital malformations).

3. The examination was performed in a supine, slightly left lateral tilted position through the examination to avoid supine hypotension.
4. Doppler flow velocity waveforms (FVW) studies were done with pulsed-wave Doppler and real time color flow localization of the umbilical arteries and Middle cerebral artery Doppler. Doppler velocimetry of the UA, MCA and DV was performed using a color Doppler system with curvilinear trans-abdominal probe.
5. We attempted to achieve an angle close to 0 degrees between the Doppler ultrasound beam and the direction of blood flow in each vessel. In spite of the coiling of the UA, in the appropriately chosen segment of cord it is possible to place the sample gate parallel to the direction of blood flow.
6. The umbilical artery Doppler and Middle cerebral artery Doppler indices from at least 3 consecutive waveforms were obtained and averaged to determine the resistance index (RI) and PI of the umbilical and Middle cerebral artery.
7. Amniotic Fluid Index method: Uterus was divided in to four quadrants using the maternal sagittal midline vertically and an arbitrary transverse line approximately half way between the symphysis pubis and the upper edge of the uterine fundus. The transducer was kept parallel to the maternal sagittal plane and perpendicular to maternal coronal plane throughout. The deepest unobstructed and clear pocket of amniotic fluid was visualized and the image was frozen, the ultrasound calipers were manipulated to measure the pocket in a strictly vertical direction.
8. The process was repeated in each of the four quadrants and the pocket measurement was summed as amniotic fluid index and then was compared with standard values. More than 25 cm value was recorded as polyhydramnios and value less than 5cm was recorded as oligohydramnios, normal 8-25, Low normal 5-8.

Laboratory investigations:

Blood samples were drawn for routine laboratory investigations. Complete blood picture (hemoglobin levels, TLC, platelet count) was assayed, Blood creatinine, aspartate transaminase (AST), alanine transaminase (ALT), electrolytes (Na, K) were assayed.

The tests were sent for analysis in Zagazig university hospital laboratories and the results were compared between the two groups (good neonatal outcome, poor neonatal outcome).

Neonatal assessment: Adverse (or abnormal) neonatal outcome was defined as any neonatal complications such as:

- Neonatal death.
- Low Apgar score (1-5-10 minute).
- Low birth weight (birth weight below the 10th percentile).
- Neonatal intensive care unit admission.

Primary outcomes:

Assessing the association between the abnormal Doppler indicies and the adverse neonatal outcome.

Results

Age distribution among studied groups

	Hypertensive Group (N=50)	Non Hypertensive Group (N=50)	t	P
Age	29.04±5.12	28.82±4.89	0.219	0.827
GA first examination	33.76±3.04	35.62±1.67	-3.787	0.00**
GA delivery	35.56±.2.71	37.4±1.44	-4.236	0.00**

There was no significant difference between groups

SBP and DBP distribution between studied groups

	Hypertensive Group	Non Hypertensive Group	t	P
SBP	157.0±7.21	119.5±6.32	27.632	0.00**
DBP	102.6±8.82	73.5±5.82	19.467	0.00**

Bl pressure significantly higher among cases

Intra uterine growth retardation distribution between groups

			Group		Total	X^2	P
			Non Hypertensive Group	Hypertensive Group			
IUGR	**No**	**N**	50	38	88	13.63	0.00**
		%	100.0%	76.0%	88.0%		
	Yes	**N**	0	12	12		
		%	0.0%	24.0%	12.0%		
Total		**N**	50	50	100		
		%	100.0%	100.0%	100.0%		

Hypertensive group significantly higher regard IUGR rate

Other outcome parameters

			Group		Total	X^2	P
			Non Hypertensive Group	Hypertensive Group			
Preterm	**No**	**N**	43	25	68	14.89	0.00**
		%	86.0%	50.0%	68.0%		
	Yes	**N**	7	25	32		
		%	14.0%	50.0%	32.0%		
NICU	**No**	**N**	46	31	77	12.7	0.00**
		%	92.0%	62.0%	77.0%		
	Yes	**N**	4	19	23		
		%	8.0%	38.0%	23.0%		
DEATH	**No**	**N**	50	48	98	2.04	0.15
		%	100.0%	96.0%	98.0%		
	Yes	**N**	0	2	2		
		%	0.0%	4.0%	2.0%		
Total		**N**	50	50	100		
		%	100.0%	100.0%	100.0%		

Hypertensive group significantly higher

Comparison between case and control regard Doppler and AFI

	Hypertensive Group	Non Hypertensive Group	t	P
DVPI	1.14±24	0.93±0.16	5.161	0.00**
UARI	1.08±0.22	0.91±0.1	4.932	0.00**
MCARI	0.63±0.11	0.62±0.04	0.260	0.795
AFI	12.32±3.8	16.88±2.43	-5.985	0.00**

Cases significantly higher regard DVPI & UARI but UA_PH & AFI were significantly lower in cases

APGAR and baby weight distribution between groups

	Hypertensive Group	Non Hypertensive Group	t	P
APGAR1	5.22±1.7	7.12±0.89	-6.203	0.00**
APGAR2	7.22±2.25	8.98±0.86	-5.155	0.00**
Baby Weight	2026.56±655.5	2936.0±435.0	-8.174	0.00**

Non Hypertensive Group significantly higher

Relation between IUGR and other parameters among cases only

	IUGR (N=12)	NO (N=38)	t	P
SBP	165.41±3.96	154.34±5.83	6.124	0.00**
DBP	107.91±6.2	100.92±8.91	2.523	0.015*
DVPI	1.36±0.08	1.07±0.23	4.138	0.00**
UARI	1.25±0.07	1.03±0.23	3.109	0.003*
MCARI	0.71±0.05	0.609±0.11	2.946	0.005
AFI	5.83±.64	14.36±3.43	-8.268	0.00**

IUGR significantly higher regard SBP,DBP, DVPI and UARI but significantly lower AFI

Multivariate logistic regression for independent predictors for IUGR

	P	OR	95% C.I .for	
			Lower	Upper
SBP	0.08	3.904	0.98	12.654
DBP	0.07	4.080	0.88	10.547
DVPI	0.04*	8.520	1.214	17.65
UARI	0.03*	10.000	2.321	21.357
AFI	0.087	4.698	0.745	13.65
Preterm	0.098	16.129	0.258	25.325

DVPI, UARI and UA were significant independent predictors for IUGR

Correlation

		DVPI	AFI
UARI	**r**	.883**	-.496-**
	P	.000	.000
MCARI	**r**	.645**	-.236-
	P	.000	.098
AFI	**r**	-.586-**	1
	P	.000	
APGAR1	**r**	-.284-*	.759**
	P	.046	.000
APGAR2	**r**	-.286-*	.686**
	P	.044	.000
Weight	**r**	-.224-	.403**
	P	.119	.004

DVPI sig positive correlated with UARI, MCARI But negatively with UA, AFI, APGAR1 and APGAR2, AFI negatively correlated with UARI, MCARI But positively with UA, APGAR1 and APGAR2 and weight.

Discussion

Preeclampsia is acute specific hypertension due to pregnancy (one of PIH) Occurring only in human female during pregnancy. Characterized by hypertension with proteinuria and/or edema in the second half of pregnancy (except with vesicular mole) or early puerperium, mortality related to pregnancy (Cunningham et al., 2005). Severe placental insufficiency is related to early and extreme growth restriction. Serial Doppler measurements of umbilical artery, middle cerebral artery and ductus venosus are commonly used for monitoring compromised pregnancies. The majority of the severely compromised fetuses have pathological venous velocimetry, most notably an increased pulsatility in the ductus venosus as signs of impaired myocardial function.

Among the studied adverse perinatal outcomes indicators, RDS is exactly the one more closely related to gestational age, more so than the situation of chronic intrauterine hypoxemia. It is therefore clear that the increase in risk of RDS in cases with alterations at Doppler is mostly due to the premature interruption of pregnancy induced by the Doppler result than the hypoxia condition of the fetus. It would be very attractive if the assessment of the fetal status were more important than the gestational age effects on perinatal outcomes, so that the moment of delivery could be based on the tests of fetal assessment.

According to Hecher et al., DV does not change before NST all the time; but the majority of the authors describe the DV Doppler velocimetry as indicating changes before modifications in other biophysical tests. At present, the DV seems to be one of the best vessels to monitor in compromised fetuses, helping to decide when to deliver.

Several authors have demonstrated that venous Doppler, and in particular the DV, is capable of predicting adverse perinatal results. However, there are few studies on the prediction of neonatal acidosis using DV Doppler and there is no consensus on which parameter and cut-off value to use for this prediction. The importance of this prediction lies in the fact that fetal metabolic acidosis is the terminal event before death in growth-restricted fetuses.

In the last decade, several studies, using cordocentesis correlated abnormal DV Doppler and fetal acidosis. However, owing to the higher risks of complications in these already compromised fetuses, cordocentesis has not become the part of standard care in the management of these cases. Rizzo et al., [18] calculated an area under the ROC curve for the prediction of hypoxemia using the DV ratio of the S/atrial systole (A) 0.66 with 72% sensitivity and 60% specificity. Data of current study indicate that for acidosis at birth a cut-off of 0.29 for the DV RI has 100% sensitivity, 57% specificity and 80% accuracy. Also cases with DV RI >0.29 were more than 3 folds likely to be involved in neonatal acidosis as those with level <0.29.

Romero et al.,[14] showed that the MCA PI has long been considered the gold standard for the assessment of fetuses with IUGR. Findings, though, suggest that not only does the MCA peak systolic velocity (PSV) complement the information provided by the MCA PI, but that it actually provides clearer information than does the MCA PI. In IUGR fetuses with an abnormal MCA PI and a normal MCA PSV, the IUGR condition is less severe than in cases in which both parameters are abnormal. However, when the IUGR condition intensifies, the MCA PSV increases and becomes abnormal.

Abnormal venous Doppler may support the decision to deliver, since there is an undeniable association between this finding and acidosis at birth, as this and other studies point out. However, as with all generalizations, caution must be exercised, especially because the population analyzed in this study was very heterogeneous, including pregnancies between 36 and 41 weeks of gestation and the variable degree of placental insufficiency. While abnormal DV Doppler velocimetry is closely correlated with neonatal acidosis, distress and death, it has not been tested in the prediction of other neonatal complications.

Many studies have been done to show the association of amniotic fluid index with some adverse perinatal outcomes and, in most findings, the occurrence of maternal and fetal complications was reported more often in pregnancies with borderline AFI than in those with normal AFI. With regard to the use of DV and the timing of delivery, there are neither data

nor consensus among clinicians. This is the subject of the 'trial of randomized umbilical and fetal flow in Europe', which aims to inform clinicians if delivery is best performed when early DV changes are seen or if delivery is best postponed until late venous changes are encountered.

The DV Doppler acts as a marker of cardiovascular deterioration in response to FGR, specifically in cases of early-onset FGR, where the DV typically becomes abnormal after an elevation of the PI in the UA. Evidence suggests that an abnormal DV waveform (absence or reversal of the A-wave, as demonstrated in Fig. 4) has the potential to predict fetal acidaemia and stillbirth, and that it is the strongest single predictor of the risk of fetal death in early-onset FGR.

The predictive ability of an abnormal DV is further revealed in its correlation with reduced fetal heart rate variability on cardiotocogram and corresponding abnormalities in the fetal biophysical profile score. A 2010 systematic review of the available literature suggests that an abnormal DV Doppler has a moderate accuracy for predicting compromise of fetal and neonatal wellbeing, and of perinatal mortality in pregnancies that are affected by placental insufficiency.

A tool that has moderate accuracy for predicting compromise or death does not equate with a tool that should be used for surveillance in FGR. Indeed, there are no systematic reviews of effectiveness of venous Doppler as a surveillance tool. This is in contrast to UA Doppler where there are randomised controlled trials and systematic reviews indicating its use as a surveillance tool. It is currently recommended by RCOG guidance that the DV Doppler should be used for the surveillance and timing of delivery of the preterm growth-restricted fetus with an abnormal UA Doppler, provided that the fetus is viable and steroids have been administered. The level of evidence for this is classified as a 'good practice point'.

In the present study, the maternal and fetal complications in women with low normal AFI were compared with normal AFI among 50 pregnant women in Zagagig University Hospitals which confirmed the increased adverse perinatal outcomes in women with AFI. Findings indicated that maternal outcomes such as preterm delivery and labor induction in women with low normal AFI were considerably higher than those in normal group and that was consistent with the findings in some other studies with the same results.

The present study showed no statistical differences between the ratios of gravidity and parity in the two study groups; whereas, in Gumus et al., and Voxman et al., [16] study, the groups were similar with respect to maternal age, gravidity and parity. Also, the present study analysis showed no significant differences between the two groups in terms of normal and pre-eclamptid cases that were consistent with the results of Gumus et al., [17] However, there were a significantly higher percentage of NICU admission in patients with normal AFI than in those with oligohydramnios. That appeared to be attributable to the higher percentage of women with diabetes in the normal AFI group.

In high-risk pregnancies, DV velocimetry, AFI and a biophysical profile are widely accepted methods of antenatal fetal assessment. Several studies have demonstrated that in preeclamptic pregnancies a reactive non-stress test or a normal biophysical profile before delivery can reliably predict normal perinatal outcome, as defined by survival, high Apgar scores or normal neonatal metabolic balance.

Assessment of the DV, which plays a fundamental role in fetal hemodynamics, as a method for fetal monitoring in high-risk pregnancies, including preeclamptic pregnancies, has been garnering interest. The DV is a small vein connecting the umbilical vein to the left side of the inferior vena cava near the entrance to the heart, and directswell-oxygenated blood via the foramen ovale into the left atrium and the left ventricle. The flow can be altered in several fetal conditions, such as fetal acidemia and cardiac function abnormality, which are known to be associated with preeclamptic pregnancies.

In our study The ability of an abnormal DV Doppler index to predict adverse perinatal outcome was therefore 32%. Of pregnancies with a normal DV-PVIV, 12.3% had an adverse perinatal outcome; therefore, the difference was statistically significant. Comparing assessment of Doppler velocimetry of the DV with a

previous report that assessed Doppler velocimetry of the umbilical artery, we found better sensitivity (53.3% vs. 30%) for Doppler velocimetry of the DV to predict adverse pregnancy outcome.

Both Hecher et al., and Rizzo et al.,[18] reported that fetal acidemia correlated significantly with elevated venous Doppler indices in both the DV and inferior vena cava. Fetal cardiac abnormalities – both congenital structural abnormalities and myocardial hypertrophy with ventricular dysfunction – are prevalent in high risk pregnancies.

Despite the encouraging findings of this study, we feel that the use of DV Doppler velocimetry for screening purposes cannot yet be universally recommended, the sensitivity and specificity being unsatisfactory for routine use. In our study, nearly half of the pregnancies with an adverse outcome failed to be detected using this

method of assessment and almost two-thirds of pregnancies with an abnormal DV result had normal pregnancy outcomes. One of the limitations of our study was its small sample size. On power analysis, the sample size had only 54% power to identify a 50% difference in the two groups.

Fetal venous Doppler studies represent valuable diagnostic techniques that can influence the management on intrauterine growth restricted fetuses as it helps in identification of the fetuses at risk for perinatal complications and helps in prediction of neonatal complications.

Conclusion

We can conclude that ductus venosus Doppler waveform was a good predictor of perinatal outcome in cases complicated by preeclampsia, as ductus venosus pulsatility index of veins (DV-PIV) and frequency of reversed a wave in ducus venosus Doppler waveform was significantly correlated with adverse neonatal outcome at delivery.

MCA and UA Doppler indices are good utilities for the assessment of fetal wellbeing and prediction of neonatal outcome in preeclamptic pregnancies.
Abnormal UA wave pattern can predict an adverse neonatal outcome.

AFI below 5 is predictive for poor neonatal outcome.

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