Case Report

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Fetal Venous Doppler Study for Evaluation of Fetuses with Non-Immune Hydrops Fetalis

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ABSTRACT

Objective: *The aim of this study was to evaluate the role of inferior vena cava, ductus venosus, and intrahepatic portion of umbilical vein Doppler in evaluation of cases of nonimmune fetal hydrops.*

Material and Method: *This study was conducted at the Department of Obstetrics and Gynecology, faculty of medicine, Alexandria University on 37 pregnant females in second and third trimester pregnancy selected from the attendees of El-Shatby Maternity university hospital. The cases were allocated into 2 main groups: group 1: twenty seven pregnant women with nonimmune fetal hydrops. Group 2: ten normal pregnant women without non- immune fetal hydrops (control group). We excluded from our study cases of immune fetal hydrops.We studied preload index of inferior vena cava, preload index and A wave of ductus venosus, and intrahepatic umbilical vein maximal velocity.*

Result: *Our results showed the presence of high statistical significant correlation between abnormally elevated preload index of inferior vena cava, ductus venosus and abnormal A wave of ductus venosus and nonimmune fetal hydrops group. There were also high statistical significant correlation between intrahepatic umbilical vein decreased maximal velocity and nonimmune fetal hydrops. These changes of the velocimetry in the Inferior vena cava, Ductus venosus, and Intrahepatic umbilical vein corresponding to changes in cardiac function and could be of value in predicting prognosis and outcome of pregnancy.*

Conclusion: *Doppler velocimetry in the IVC, DV, and intrahepatic portion of UV is a useful tool in the workup of hydropic fetuses.*

Introduction

Fetal hydrops means abnormal presence of extracellular fluid in at least two fetal body compartments. These fluid collections include scalp and body wall edema, pericardial effusion, pleural effusions, and ascites; Placentomegaly, and polyhydramnios may be associated [1].

After introduction of Rh (D) immune globulin the prevalence of Rh (D) alloimmunization and associated hydrops has dramatically decreased; However, NIHF now accounts for almost 90 percent of hydrops cases [2,3].

The pathogenesis of NIHF remains unclear, and likely depends in part, on the underlying disorder. NIHF is the end result of one or, more abnormalities [4-6].

Mirror syndrome reflects the maternal manifestations that can occur at any time during the antepartum period and may persist postpartum [7]. Clinical manifestations are similar to that of severe preeclampsia [8]. In contrast to preeclampsia, the maternal hematocrit is often low due to hemodilution and amniotic fluid volume is often high (polyhydramnios) rather than low (oligohydramnios), and the fetus always shows signs of hydrops

[8,9]. NIHF should be seen as a symptom or clinical phenotype rather than as a disorder, and considered as a non-specific, end-stage status of a wide variety of disorders [2,3].

These include fetal disorders (presented below in table (1)), maternal diseases (e.g., severe maternal anemia, diabetes and maternal indomethacin use) and placental/cord abnormalities (e.g., chorioangioma angiomyxoma of the cord, and chorionic vein thrombosis) [10]. NIHF is associated with an overall perinatal mortality rate of 50 to 98 percent [11]. Despite advances in fetal diagnosis and therapy, the mortality rate has not changed very much over the past 15 years [12].

Prognosis depends upon the etiology, the gestational age at onset, and whether pleural effusions are present [10]. Arterial Doppler waveforms are related to both input pressure and downstream vascular resistance. Fetal arterial Doppler assessment has predominantly utilized the umbilical artery [13], fetal aorta [14] and middle cerebral artery [15].

Doppler assessment of these and other, fetal arteries provides information on regional blood flow and perfusion of individual organs, as well as giving insights into the fetal circulatory state in health and disease [16]. The clinical utility of venous Doppler velocimetry is therefore greatest in fetal conditions with cardiac manifestations and/or marked placental insufficiency. These conditions include fetal growth restriction due to placental insufficiency, twin-twin transfusion, fetal hydrops, and fetal arrhythmia [16].

The development of umbilical venous pulsations in hydropic fetuses is an ominous finding associated with demise in over 70 percent of patients [17]. Therefore, venous Doppler should form part of the diagnostic assessment nonimmune fetal hydrops.

Aim of the Work

The aim of this study is to evaluate fetuses with non-immune fetal hydrops by venous Doppler study; for quantitative assessment of flow in inferior vena cava, qualitative assessment of flow in ductus venosus, and assessment of intrahepatic umbilical vein maximum velocity.

Patients and Methods

This study was conducted at the Department of Obstetrics and Gynecology, faculty of medicine, Alexandria University on 37 pregnant females in second and third trimester pregnancy selected from the attendees of El-Shatby Maternity university hospital.

They were subdivided in two groups:

- Group1: Twenty seven pregnant females with hydrops fetalis.
- Group2: Ten pregnant females with normal fetuses.

Inclusion criteria

Of cases:

In the 2nd or third trimester.

Non-immune hydrops fetalis diagnosed by ultrasonogram:

- Ascites, pleural effusion, subcutaneous oedema.
- Negative antibody screening (Indirect comb's test) in cases of fetal hydrops caused by fetal anemia evidenced by abnormally elevated peak systolic velocity in middle cerebral artery.

Exclusion criteria

Cases of Immune hydrops fetalis suspected by abnormally elevated peak systolic velocity in middle cerebral artery in cases wih RH negative, and positive antibody screening test will be excluded.

Methods

Following approval of the medical ethical committee. All cases in this study were subjected to the following regimen:

- History taking:
- General medical examination: the aim was to exclude development of mirror syndrome.
- Evaluation of pregnancy using abdominal ultrasound to assess:
- Differentiation between immune and non-immune fetal hydrops in anaemic fetal hydrops by:
- Fetal cardiac examination: for diagnosis of congenital heart disease: using 2 D, and Doppler ultrasound
- Doppler study of the following vessels:

Inferior vena cava (IVC), Umbilical vein (UV), Dctus venosus (DV).

The ductus venosus was identified using color Doppler in a right ventral mid-sagittal plane by placement of the sample volume at the initial portion of the vessel. The insonation angle, was kept below 30° [18]. The PLI value were obtained and plotted against the reference ranges [19] and compared between the two groups. The A wave described normal, or abnormal if decreased, absent, or reversed [20].

The inferior vena cava identified using color Doppler while entering the right atrium [21]. The PLI value were obtained and plotted against the reference ranges [22] and compared between the two groups. For the measurement of intrahepatic umbilical vein maximal velocity, the Doppler range-gate is placed over the intra-abdominal portion of the umbilical vein in a transverse plane of the fetal abdomen [23]. The measurements of intrahepatic umbilical vein Vmax plotted against the percentile charts for intrahepatic umbilical vein Vmax [23] and compared between the two groups.

Follow up of cases till delivery or termination of pregnancy or intrauterine fetal death

Data collection

After data collection, raw data was coded and scored, and a coding instruction manual was prepared. Data were fed to the computer and statistical analysis was performed using Statistical Package for Social Sciences (SPSS 20.0) for Windows statistical software.

Results

The mean age in study group was 27.96 ± 2.82 years, while in control group was 28.40 ± 2.76 years, there was no significant

difference between the two groups (p>0.05). The mean gestational age in study group was 22.78 ± 5.26 weeks, while in control group was 22.90 ± 4.28 weeks, there was no significant difference between the two groups regarding gestational age (p>0.05). The mean gravidity in study group was 2.30 ± 0.67, while in control group was 1.80 ± 0.92, there was no significant difference between the two groups regarding gravidity (p>0.05). The mean parity in study group was 1.22 ± 0.70, while in control group was 0.80 ± 0.92, there was no significant difference between the two groups regarding parity (p>0.05).

Fetal Age by Ultrasound, the mean fetal age in study group was 22.96 ± 5.33 weeks, while in control group was 23.48 ± 4.18weeks, there was no significant difference between the two groups regarding fetal age (p>0.05). Amniotic fluid volume by U/S, in study group the mean fluid volume was 7.13 ± 3.59, while in control group was 4.84 ± 1.23, there was significant difference between the two groups regarding the amniotic fluid volume (p <0.05). Estimated fetal weight by U/S, the mean estimated fetal weight in study group was 945.19 ± 578.93, while in control group was 749.0 ± 500.19 gm, there was no significant difference between the two studied groups regarding estimated fetal weight (p>0.05).

A wave of ductus venosus, it was normal in 14 cases (51.9%), and abnormal in 13 cases in the study group (48.1%), while in control group it was normal in all cases. There was significant difference between the two studied groups regarding A wave (p<0.05). Abnormal A wave was applied to decreased, absent, or reversed A wave.

	Study group	Control group	p
IVC PLI	0.55 ± 0.33	0.26 ± 0600	0.002*
DV PLI	0.79 ± 0.33	0.51 ± 0.10	0.003*
Umbilical V	11.0 ± 2.25	12.97 ± 2.46	0.029*

Table 1: Comparison between the two studied groups regarding (IVC PLI), DVPLI and umbilical V.

Table 1, shows the comparison between the two studied groups IVC PLI, the mean IVC PLI in study group was 0.55 ± 0.33, while in control group was 0.26 ± 0.06, there was a significant increase in IVC PLI in study group more than the control group (p<0.05), DV PLI, in study group DV PLI was 0.79 ± 0.33, while in control group was 0.51 ± 0.10, there was a significant increase in DV PLI in study group more than the control group (p<0.05)., Umbilical V, in study group the umbilical V was 11.0 ± 2. 25 while in control group was 12.97 ± 2.46, on comparing the two groups it was found there was significant increase in umbilical V velocity in control group more than the study group (p<0.05).

Regarding the history of congenital heart disease, it was found that there was 4 cases (14.8%) in study group had history of CHD, in control group it was found no cases with history of CHD. there was no significant difference between the two groups regarding history of CHD (p>0.05). The History of thalassemia, it was found that there was only one patient in study group had history of thalassemia3.70%, there was no significant difference between the two groups (p>0.05).

The History of non-immune fetal hydrops in previous pregnancy, it was found that there was two cases in study group had history of previous non-immune fetal hydrops 7.4%, there was no significant difference between the two groups (p>0.05). Regarding structural fetal abnormalities, it was found that 3cases (11.1%) had a positive finding of structural abnormalities in study group (one case with meningocele, and two cases with congenital cystic adenomatoid malformation). In control group it was found no cases with structural abnormalities. There was no significant difference between the two groups (p>0.05).

The structural cardiac abnormalities, it was found that 7 cases (25.9%) had a positive finding of structural cardiac abnormalities in study group; in control group it was found no cases with structural cardiac abnormalities. There was a significant increase in congenital heart disease in study group more than the control group. (There were two cases with atrioventricular canal, one case with ventricular septal diffect, one case with closed foramen ovale, two cases with hypoplastic left heart, and one case with transposition of great vessels).

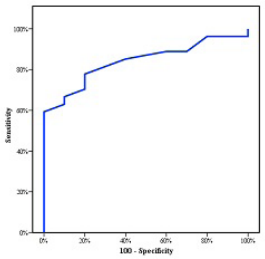
Table 2, shows the area under the curve, cut off value, sensitivity and specificity of IVC PLI in diagnosis the fetus with non-immune hydrops fetalis, it was found that the area under the curve of IVC PLI was 0.841, and the cut off value was >0.31, at this point the sensitivity was 70.37%, specificity was 80.0% and the accuracy was 72.97%. The sensitivity and specificity of DV PLI in predict the fetus with non-immune hydrops fetalis, the area under the curve was 0.824, the cut off value was >0.61, at this cut off value the sensitivity was 74.07%, specificity 80.0% and the accuracy was 75.68%. The cut off value, sensitivity and specificity of Intrahepatic umbilical vein in diagnosis the fetus with non-immune hydrops fetalis, the area under the curve was 0.739, the cut off value was >0.61, at this cut off value the sensitivity was 62.96%, specificity 80.0% and the accuracy was 67.57%.

	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
IVC PLI	>0.31	70.37	80.0	90.5	50.0	72.97
DV PLI	>0.61	74.07	80.0	90.9	53.3	75.68
Umbilical V	≤11.17	62.96	80.0	89.5	44.4	67.57

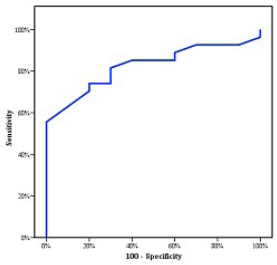
Table 2: Agreement (sensitivity, specificity) for IVC PLI to diagnose cases with non-immune fetal hydrops from normal cases.

	Number	Percent
Preterm labor (fetus died due to prematurity)	3	11.1%
Spontaneous resolution	1	3.7%
IUFD (intra uterine fetal death)	5	18.5%
Termination	18	66.7%
Total	27	100.0%

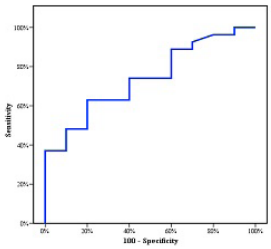
Table 3: Distribution of the studied patients regarding the fate at end of follow up.



ROC curve for IVC PLI to diagnose cases with non-immune fetal hydrops from normal cases



ROC curve for DV PLI to diagnose cases with non-immune fetal hydrops from normal cases



ROC curve for Umbilical V to diagnose cases with non-immune fetal hydrops from normal cases

Discussion

Non-immune hydrops fetalis represents a clinical end-point for numerous fetal disorders that range from good prognosis with treatment to lethal conditions [24]. One of the most important steps in managing a pregnancy complicated by nonimmune hydrops is determining the cause of the disorder [24]. The common etiologies include cardiovascular, chromosomal, and hematologic abnormalities, followed by structural fetal anomalies, complications of monochorionic twinning, infection, and placental abnormalities [25].

Many of these conditions can affect forward cardiac function and, therefore, abnormal venous Doppler waveforms. In myocardial dysfunction leading to low-output heart failure and in certain structural heart defects, right heart pressure increases, resulting in increased central venous pressure (preload) [25]. Venous Doppler studies show good accuracy when the preload is excessive in a fetus. The PLI-IVC index was first defined by Kanzaki and Chiba [26] in 1990 as the ratio between the reversed flow velocity from the right atrium and the forward velocity of the IVC; its value was found to increase under high preload conditions. Generally, the PLI-IVC decreases gradually with advancing gestational age [22,27,28].

Evaluation of the PLI-IVC or the percentage of reversed flow in the IVC has been reported to be useful in clinical decision making or for evaluation of the fetal circulatory state in cases of fetal hydrops. Abnormal venous Doppler appears to be more frequent in low-output hydrops compared to high-output hydrops [29-31].

Interestingly, high-output hydropic fetuses with anemia can show normal or even low preload index (PLI) and pulstility index (PIV) in the Ductus venosus, despite a hyperdynamic circulation or hypervolemia [31]. This suggests that hydrops fetalis in the early stages of anemia is not primarily due high-output cardiac decompensation. Here, the increase in cardiac output leads to a decrease in forward flow resistance in the Ductus venosus, and is an expression of initial fetal compensation [31].

An abnormality in Ductus venosus Doppler waveform typically reflects a cardiac defect confirmed at echocardiogram [32] and chromosomal abnormalities that account for approximately 10–15% of hydrops cases. Hydrops in fetuses with an abnormal karyotype is usually related to either an associated cardiac defect or a defect in lymphatic flow [24].

The umbilical venous Doppler flow pattern is usually described as mildly phasic, low velocity flow. With increases in central venous pressure, umbilical venous flow may reverse altogether leading to placental swelling [33] notching is first seen at end-diastole, corresponding to atrial contraction. In cases of severe congestive heart failure or hydrops fetalis, venous pulsations may be seen [34].

The aim of the work was to evaluate fetuses with non-immune fetal hydrops by venous Doppler study; for quantitative assessment of flow in inferior vena cava, qualitative assessment of flow in ductus venosus, and assessment of intrahepatic umbilical vein maximum velocity.

This study was conducted at the Department of Obstetrics and Gynecology, faculty of medicine, Alexandria University on 37 pregnant females in second and third trimester pregnancy selected from the attendees of El-Shatby Maternity university hospital.

All cases were subjected to thorough medical and obstetric history and examination Rh typing and indirect comb's test was done to all members of the study group to exclude immune fetal hydrops.

All cases underwent ultrasonography to determine gestational age, and diagnose fetal hydrops. Echocardiography was done to diagnose structural cardiac abnormalities, and middle cerebral artery peak systolic velocity was measured by Doppler ultrasound to diagnose anaemic fetal hydrops. Inferior vena cava, Ductus venosus and intrahepatic umbilical vein Doppler was done.

The cases were allocated into 2 main groups: group 1: twenty seven pregnant women with fetal hydrops. Group 2: ten normal pregnant women without fetal hydrops (control group).

We studied Doppler indices of Inferior vena cava, Ductus venosus and intrahepatic umbilical vein for evaluation of outcome.

Our results revealed significant statistical difference between the two studied groups with increase in inferior vena cava preload index (IVC-PLI) in non-immune hydrops fetalis cases (group 1) were p value of < 0.002.

Watanabe e al [35] conducted study on 101 cases on non-immune fetal hydrops, 30 cases were complicated structural cardiac disease.

He found increased inferior vena cava preload index in these cases. He concluded that cardiogenic hydrops had bad prognosis as the mortality rate was 86.7%.

Hidaka, et al [36] conducted retrospective study on Five cases of prenatally diagnosed Ebstein anomaly they aimed to investigate whether the preload index of the inferior vena cava (PLI-IVC) is of diagnostic value in predicting hydropic changes in fetuses with Ebstein anomaly.

They founded the PLI-IVC was high in all the cases. In 2 cases, PLI-IVC values tended to increase gradually before hydropic changes were recognized. In the cases without hydrops, PLI-IVC values exhibited a nonlinear trend throughout gestation and did not show any apparent increase.

They concluded that the upward trend of the PLI-IVC could be considered a sign of cardiac failure. Actually, an increase in PLI reflects an increase in central venous pressure. Okamura et al. [37] studied the relationship between umbilical venous pressure (UVP) by cordocentesis and PLI in 50 compromised fetuses There was a significant correlation between UVP and PLI. They concluded that IVC-PLI is an alternative parameter to central venous pressure and a useful index for assessment of fetal cardiac function.

Given its proximity to the heart, abnormalities in the ductus venosus Doppler flow pattern may be seen prior to any changes within the umbilical vein In fetuses with underlying congestive heart failure, the a wave velocity, corresponding to atrial contraction, decreases initially and then may become reversed [34].

Abnormal venous flow, in both the Ductus venosus (absent/reversed A wave) and the umbilical vein (pulsations), is strongly related to mortality in pregnancies complicated by fetal hydrops [17,30,38] with perinatal mortality rates as high as 79% [30].

Our study demonstrated that, there were high statistical significant correlation between Ductus venosus increased preload index, and abnormal a wave and nonimmune fetal hydrops cases (group 1) with p value < 0.003, 0.007 respectively.

Hofstaetter et al [30] conducted a prospective study on one hundred cases to examine blood flow velocity in different types of fetal hydrops and its value in the prediction of outcome of pregnancies.

Mortality was noted in 51 cases of which 19 were by termination of pregnancy. Mortality in the 30 with normal venous blood velocity was 35%, but 58% in cases of abnormal Doppler. DV blood velocities were recorded in 34 cases, and were strongly related to mortality.

UV pulsations were noted in 49 fetuses and were significantly related to mortality. Mortality and abnormal venous velocities were most frequent in the low-output hydrops group (79% and 75%, resp). And concluded that abnormal venous blood velocity is related to mortality in pregnancies complicated by fetal hydrops.

Fetal systemic venous blood flow pulsates with a typical flow pattern directly related to increased central venous pressure [39,40].

Increased central venous (right atrial) pressure will therefore alter the venous blood flow pattern with especially decreased diastolic blood flow velocities and often augment reversal of flow in end-diastole at the time of atrial contraction [40].

Increased central venous pressure or hypoxia will facilitate opening of the ductus venosus and thus transmission of central venous pulsations into the umbilical vein. The pattern of UV pulsations will depend on the degree of DV opening [40-42].

Pulsating blood velocity in the umbilical vein was defined as a decrease in velocity by more than 15% of the maximal velocity [43].

Our study revealed that, there were high statistical significant correlation between decreased maximal velocity in intrahepatic umbilical vein and non-immune fetal hydrops cases (group 1) with p value < 0.029.

Tongosong et al [42] conducted study on 69 cases of non-immune fetal hydrops. The objective of the study was to compare fetal venous Doppler flow reflecting cardiac function in fetuses with hydrops fetalis between a group of congenital heart defect (low cardiac output) and a fetal anemia group (high cardiac output).

The peak velocity index, preload index, and the pulsatility index of the DV were significantly low in the high-output group, whereas they were significantly high in the low-output group. The umbilical vein pulsations were found in 78.9% of the fetuses with low-output hydrops fetalis but only 28.0% of fetuses in the high output.

UV pulsations and changes in diastolic blood velocities in the fetal inferior vena cava have been related to heart failure and mortality [38,44].

Conclusions

The inferior vena cava vein preload index is abnormally elevated in cases of nonimmune fetal hydrops. And have significant relation with poor prognosis in cases of nonimmune fetal hydrops. Ductus venosus Doppler indices (PLI, A wave) are significantly abnormal in cases of nonimmune fetal hydrops. Intrahepatic umbilical vein maximal velocity is significantly decreased in nonimmune fetal hydrops. And is associated with poor prognosis in these cases.

However, the use of venous Doppler for assessment of non-immune fetal hydrops is beneficial in predicting the cause of fetal hydrops, and the fetal outcome.

Recommendations

- Venous Doppler must be done for assessment of all cases with nonimmune fetal hydrops as a noninvasive method for

diagnosis of the possible causes, and to decrease the scope of invasive methods for diagnosis of nonimmune fetal hydrops.

- Venous Doppler must be done in combination with middle cerebral artery Doppler for evaluation of cases with nonimmune fetal hydrops to differentiate between anaemic and non anaemic nonimmune fetal hydrops to facilitate interference by therapeutic intervention or by delivery if near full term.
- All cases with abnormal venous Doppler should undergo complete anomaly scan and fetal echocardiogram
- Further studies are needed to study venous Doppler in nonimmune fetal hydrops according to the pathophysiological causes of nonimmune fetal hydrops and its relation to neonatal outcome.

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